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(54) Imidazonaphthyridine derivatives

Imidazonaphthyridinderivate

Dérivés d'imidazonaphtyridines

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(56) References cited:
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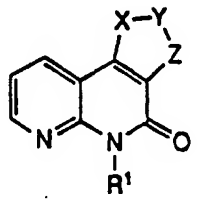
Description

The present invention relates to novel imidazonaphthyridine derivatives having a 1H,5H- or 3H,5H-imidazo[4,5-c][1,8]naphthyridin-4-one skeleton and showing an anti-inflammatory activity, an anti-allergic activity and a broncho-dilative activity.

Imidazo[4,5-c]quinoline derivatives having a broncho-dilative and antiviral activity are disclosed in Japanese Published Unexamined Patent Application No. 123488/85 (U.S.P. Nos. 4,698,348 and 4,689,338 and EP-A-145340). However, 1H,5H- or 3H,5H-imidazo[4,5-c][1,8]naphthyridin-4-one derivatives and their pharmacological activity are unknown.

An object of the present invention is to provide novel imidazonaphthyridine derivatives having a potent anti-inflammatory, anti-allergic and broncho-dilative activity.

This object has been achieved by imidazonaphthyridine derivatives represented by formula (I):



(I)

wherein R^1 represents lower alkyl or substituted or unsubstituted phenyl or naphthyl, and X-Y-Z represents

wherein R^2 represents hydrogen, lower alkyl, alkenyl, styryl or cinnamyl ,or-$C(R^5)H$-$(CH_2)_n$-R^4 (wherein R^4 represents substituted or unsubstituted phenyl or naphthyl, substituted or unsubstituted pyridyl, substituted or unsubstituted furyl, hydroxy-substituted lower alkyl, lower alkanoyloxy, morpholino, lower alkanoyl, carboxy, lower alkoxycarbonyl, cycloalkyl, hydroxy, lower alkoxy, halogen or NR^6R^7 wherein R^6 and R^7 independently represents hydrogen or lower alkyl; R^5 represents hydrogen, lower alkyl, or phenyl; and n represents an integer of 0 to 3); and R^3 represents hydrogen, mercapto, hydroxy, lower alkyl, or phenyl or naphthyl and pharmaceutically acceptable salts thereof.

The compounds represented by formula (I) are hereinafter referred to as Compounds (I); the same applies to the compounds of other formula numbers.

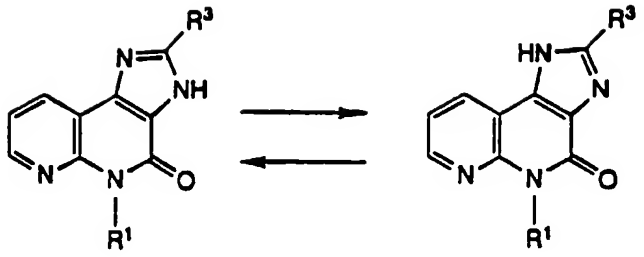
In the definitions of the groups in formula (I), lower alkyl and the alkyl moiety in the hydroxy-substituted lower alkyl and the lower alkoxy mean a straight-chain or branched alkyl group having 1 to 8 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl, hexyl, heptyl and octyl.

Alkenyl means an alkenyl group having 2 to 6 carbon atoms such as vinyl, allyl, propenyl, butenyl and hexenyl. Lower alkanoyl and the alkanoyl moiety in the lower alkanoyloxy mean a straight-chain or branched alkanoyl group having 1 to 6 carbon atoms such as formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl and hexanoyl.

cycloalkyl means a cycloalkyl group having 3 to 8 carbon atoms such as cyclopropyl, cyclopentyl, cyclohexyl and cyclooctyl.

The phenyl, naphthyl, pyridyl and furyl group may be substituted by one to three substituents which are the same or different. Examples of the substituents are lower alkyl, lower alkoxy, nitro, lower alkoxycarbonyl and halogen. The definitions of the lower alkyl and the alkyl moiety in the lower alkoxy and the lower alkoxycarbonyl are the same as those of the lower alkyl and the alkyl moiety in the hydroxy-substituted lower alkyl and the lower alkoxy described above. Examples of the halogen include fluorine, chlorine, bromine and iodine.

Compounds (I) wherein R^2 is hydrogen are present as Compounds (I-1) and/or (I-2),which are tautomers, but in the following description, they are collectively referred to as Compounds (I-1).



(I-1) (I-2)

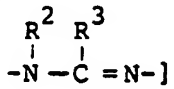
The pharmaceutically acceptable salts of Compounds (I) include acid addition salts, metal salts, ammonium salts, organic amine addition salts, and amino acid addition salts. As the pharmaceutically acceptable acid addition salts of Compounds (I), inorganic acid addition salts such as hydrochloride, sulfate and phosphate, and organic acid addition salts such as acetate, maleate, fumarate, tartrate and citrate may be mentioned. As the pharmaceutically acceptable metal salts, alkali metal salts such as sodium salt and potassium salt, alkaline earth metal salts such as magnesium salt and calcium salt, aluminum salt, and zinc salt may be mentioned. As the pharmaceutically acceptable organic amine addition salts, salts with morpholine and piperidine may be mentioned, and as the pharmaceutically acceptable amino acid addition salts, salts with lysine, glycine and phenylalanine may be mentioned.

The processes for preparing Compounds (I) are described below.

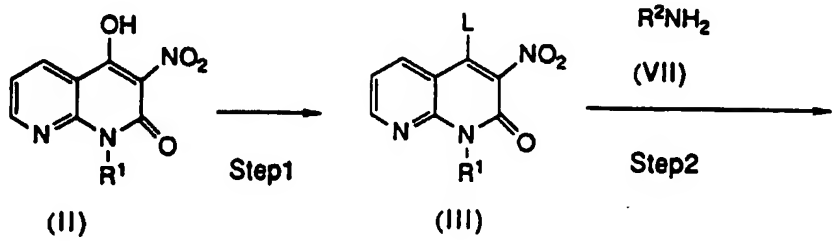
In the following processes, in cases where the defined groups change under the conditions shown or are inappropriate for practicing the processes, the processes can be readily carried out by applying thereto means conventionally used in organic synthetic chemistry, for example, protection of functional groups and elimination of protecting groups.

Process 1

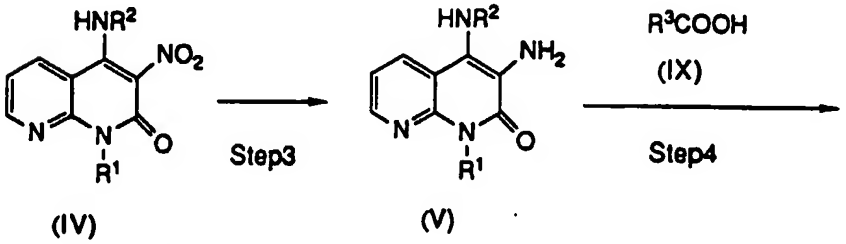
Compound (Ia) [Compound (I) wherein X-Y-Z is



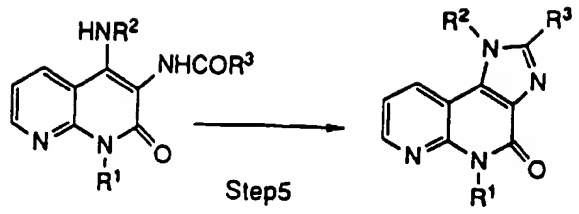
] can be obtained by the following reaction steps.



(II) (III)



(IV) (V)



(VI) (Ia)

In the above formulae, L represents a leaving group, and R^1, R^2 and R^3 have the same significances as defined above.

Examples of the leaving group represented by L include a halogen atom such as chlorine, bromine or iodine, alkylsulfonyloxy such as methanesulfonyloxy, and arylsulfonyloxy such as phenylsulfonyloxy or p-toluenesulfonyloxy.

The starting compound (II) can be synthesized by a known method [J. Heterocyclic Chem., 22, 193 (1985)] or by the method shown in Reference Example 1.

(Step 1)

Compound (IIIa) [Compound (III) wherein L is sulfonyloxy] can be obtained by allowing Compound (II) to react with sulfonyl chloride in the presence or absence of a base and a solvent.

Examples of the base are alkali metal carbonates such as potassium carbonate and sodium carbonate, alkali metal hydrides such as sodium hydride, alkali metal alkoxides such as sodium methoxide and sodium ethoxide, and alkylamines such as triethylamine.

As the reaction solvent, those which are inert to the reaction, for example, ethers such as tetrahydrofuran and dioxane, amides such as dimethylformamide, alcohols such as methanol and ethanol, hydrocarbons such as xylene, toluene, n-hexane and cyclohexane, haloalkanes such as chloroform and carbon tetrachloride, and dimethylsulfoxide, sulfoxide, may be used alone or in combination.

As the sulfonyl chloride, alkylsulfonyl chloride such as methanesulfonyl chloride, arylsulfonyl chloride such as p-toluenesulfonyl chloride, etc. may be used.

The reaction may be carried out at 0 to 100°C and completed in 5 minutes to 24 hours.

Compound (IIIb) [Compound (III) wherein L is halogen] can be obtained by allowing Compound (II) to react with a halogenating agent in the presence or absence of a solvent, if necessary, in the presence of a base.

The same base and solvent as mentioned above may be used.

As the halogenating agent, thionyl chloride, phosphorus oxychloride, phosphorus pentachloride, phosphorus tribromide, etc. may be used.

The reaction may be carried out at 0 to 200°C and completed in 5 minutes to 24 hours.

(Step 2)

Compound (IV) can be obtained by allowing Compound (III) to react with amine (VII) [Compound (VII)] in the presence or absence of a solvent, if necessary, in the presence of a base.

Examples of the base are alkali metal carbonates such as potassium carbonate and sodium carbonate, alkali metal hydrides such as sodium hydride, alkali metal alkoxides such as sodium methoxide and sodium ethoxide, and alkylamines such as triethylamine.

As the reaction solvent, those which are inert to the reaction, for example, ethers such as tetrahydrofuran and dioxane, amides such as dimethylformamide, alcohols such as methanol and ethanol, hydrocarbons such as xylene, toluene, n-hexane and cyclohexane, haloalkanes such as chloroform and carbon tetrachloride, and dimethylsulfoxide may be used alone or in combination.

The reaction may be carried out at 0 to 100°C and completed in 5 minutes to 24 hours.

(Step 3)

Compound (V) can be obtained by reducing Compound (IV) in a solvent.

Reduction is carried out, for example, by catalytic reduction using a catalyst such as palladium/carbon or platinum oxide; reduction using a metal such as iron or zinc; and reduction using a metal sulfur derivative such as sodium hydrosulfite.

As the reaction solvent, those which are inert to the reaction, for example, ethers such as tetrahydrofuran and

dioxane, amides such as dimethylformamide, alcohols such as methanol and ethanol, acids such as hydrochloric acid, acetic acid and sulfuric acid, and water, may be used alone or in combination.

The reaction may be carried out at 0 to 100°C and completed in 5 minutes to 24 hours.

(Step 4)

Compound (VI) can be obtained by allowing Compound (V) to react with carboxylic acid (IX) [Compound (IX)] or a reactive derivative thereof.

When Compound (IX) is used, it is preferred to carry out the reaction in the presence of a condensing agent. As the condensing agent, thionyl chloride, N,N'-dicyclohexylcarbodiimide (DCC), polyphosphoric acid, etc. may be used. Examples of the reactive derivative are acid halides such as acid chloride and acid bromide, acid anhydrides, mixed acid anhydrides formed with ethyl chlorocarbonate, isobutyl chlorocarbonate, etc., activated esters such as p-nitrophenyl ester and N-oxysuccinimide ester, and ortho esters.

The reaction may be carried out at -10 to 50°C and completed in 5 minutes to 24 hours.

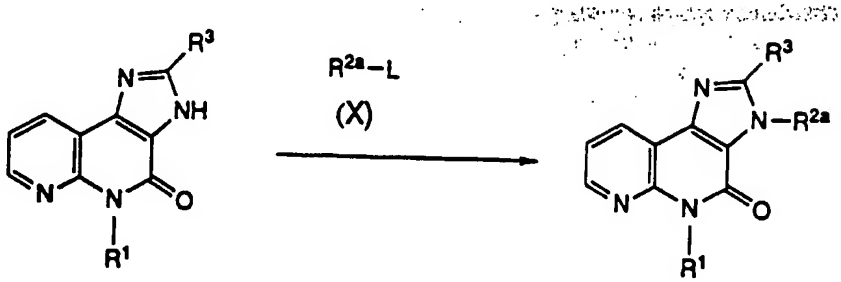
(Step 5)

Compound (Ia) can be obtained by subjecting Compound (VI) to reaction in the presence or absence of a solvent, if necessary, in the presence of a cyclizing agent.

Examples of the reaction solvent include hexamethylphosphoramide, diphenyl ether, glycerine triethyl ether, butyl ether, isoamyl ether, diethylene glycol, triethylene glycol, and Dowsam A (Dow Chemical Co., Ltd.). Examples of the cyclizing agent include polyphosphoric acid, polyphosphoric acid ester, sulfuric acid, acetic acid, phosphorus pentoxide, phosphorus oxychloride, phosphorus trichloride, phosphorus tribromide, phosphorus pentachloride, and thionyl chloride.

The reaction may be carried out at 50 to 250°C, preferably 100 to 250°C,and completed in 5 minutes to 24 hours.

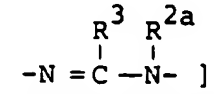
Process 2



(I-1) (Ib)

In the above formulae, R^{2a} represents R^2 as defined above with the exception of hydrogen; and R^1, R^3 and L have the same significances as defined above.

Compound (Ib) [Compound (I) wherein X-Y-Z is



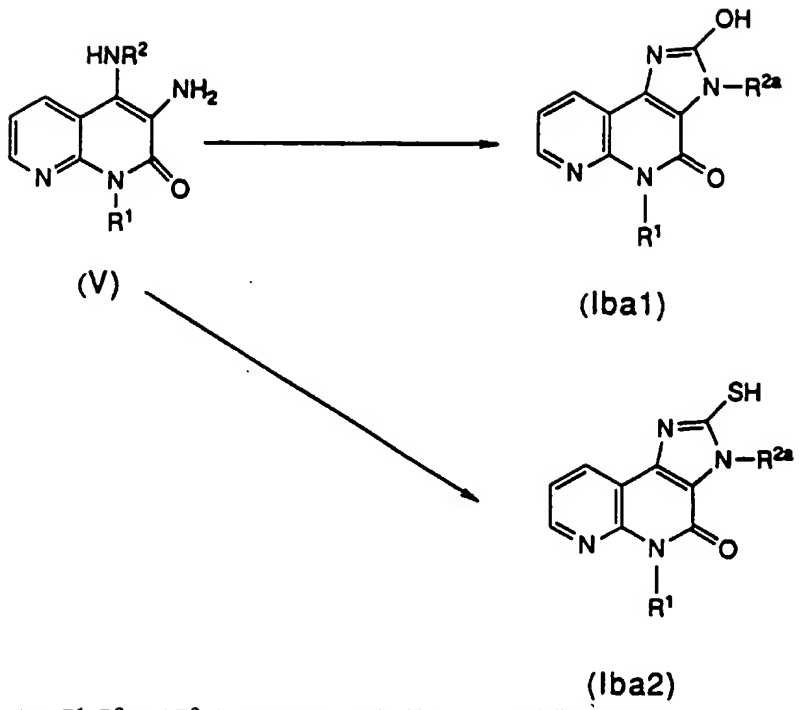
can be prepared by allowing Compound (I-1) to react with Compound (X) in the presence or absence of a solvent, preferably in the presence of a base.

The same solvent and base as in Step 1 of Process 1 ray be used.

The reaction may be carried out at 0 to 200°C and completed in 5 minutes to 24 hours.

Process 3

Compound (Iba) [Compound (Ib) wherein R^3 is hydroxy or mercapto] can also be obtained from Compound (V) obtained in Process 1 by the following method.



In the above formulae, R^1, R^2 and R^{2a} have the same significances as defined above.

Compound (Iba1) [Compound (Iba) wherein R^3 is hydroxy] can be prepared by allowing Compound (V) to react with a carbonic acid derivative, such as phosgene, carbonyldiimidazole, urea, or the like.

As the reaction solvent, those which are inert to the reaction, for example, alcohols such as methanol and ethanol, ethers such as tetrahydrofuran and dioxane, and halogenated hydrocarbons such as chloroform may be used alone or in combination.

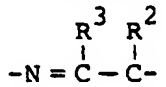
The reaction may be carried out at 0 to 150°C and completed in 30 minutes to 10 hours.

Compound (Iba2) [Compound (Iba) wherein R^3 is mercapto] can be obtained by allowing Compound (V) to react with a thiocarbonic acid derivative, such as thiophosgene, thiocarbonyldiimidazole, thiourea, or the like.

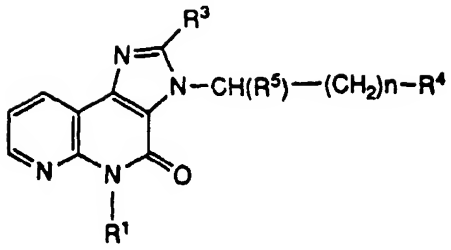
The reaction is carried out under the same conditions using the same solvent as in the process for preparing Compound (Iba1).

Process 4

Compound (Ic) is Compound (I) wherein X-Y-Z represents

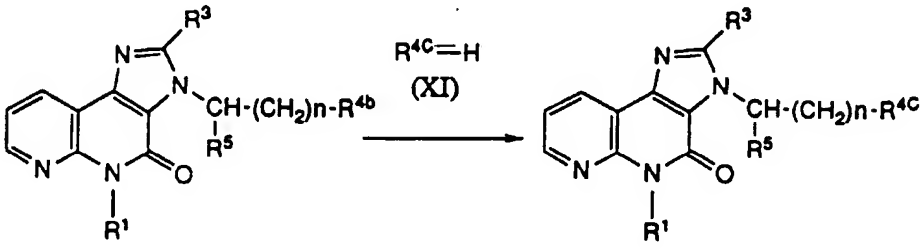


and R^2 is $-C(R^5)H-(CH_2)_n-R^4$.



(Ic)

Compound (Ic2) [Compound (Ic) wherein R^4 is NR^6R^7 or morpholino] can be obtained by the following reaction step.



(Ic1) (Ic2)

In the above formulae, R^1, R^3 and R^5 have the same significances as defined above; R^{4b} represents halogen in the definition of R^4; and R^{4c} represents NR^6R^7 or morpholino in the definition of R^4.

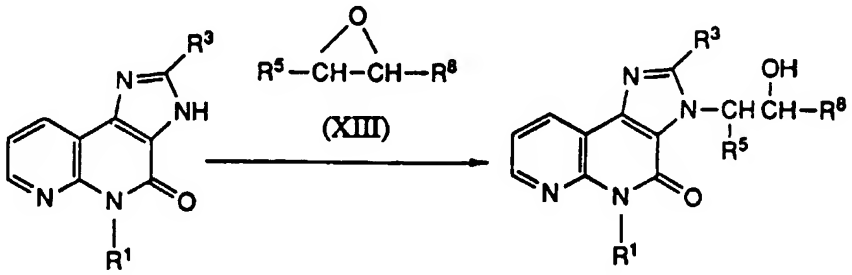
Compound (Ic2) can be obtained by allowing Compound (Ic1) to react with Compound (XI) in the presence or absence of a base and a solvent.

The same reaction solvent and base as in Step 1 of Process 1 may be used.

The reaction may be carried out at 0 to 200°C and completed in 5 minutes to 24 hours.

Process 5

Compound (Ic3) [Compound (Ic) wherein R^4 is hydroxy] can be obtained by the following reaction step.



(Ic3)

In the above formulae, R^1, R^3 and R^5 have the same significances as defined above; and R^8 is hydrogen or lower alkyl having 1 to 7 carbon atoms.

Compound (Ic3) can be obtained by allowing Compound (I-1) to react with Compound (XIII) in the presence or absence of a base and a solvent.

The same reaction solvent and base as in Process 1 may be used.

The reaction may be carried out at 0 to 200°C and completed in 5 minutes to 24 hours.

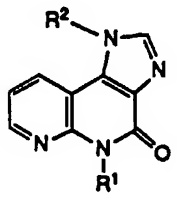
The intermediates and the desired products in the processes described above can be isolated and purified by purification means conventionally used in organic synthetic chemistry, for example, filtration, extraction, washing, drying, concentration, recrystallization and various kinds of chromatography. The intermediates can be subjected to the subsequent reaction without particular purification.

In the case where a salt of Compound (I) is desired and it is produced in the form of the desired salt, it can be subjected to purification as such. In the case where Compound (I) is produced in the free state and its salt is desired, it can be converted into its salt in a conventional manner.

Compounds (I) and pharmaceutically acceptable salts thereof sometimes exist in the form of an addition product with water or with a solvent. Such addition products are also included within the scope of the present invention.

Specific examples of Compounds (I) obtained in the respective processes are shown in Table 1.

Table1-1



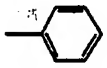
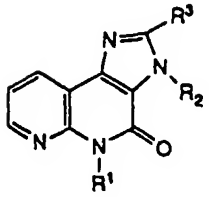
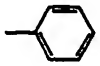
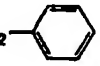
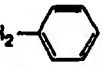
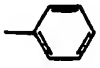
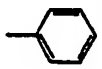
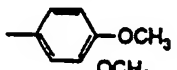
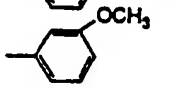
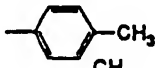
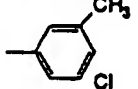
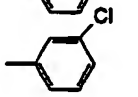
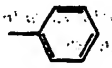
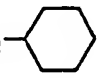
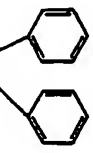
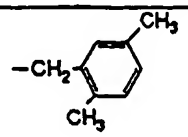
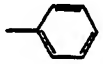
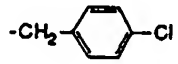
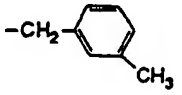
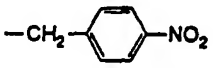
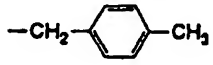
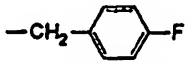
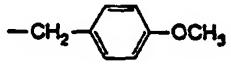
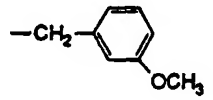
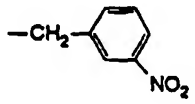
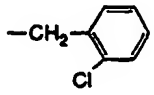
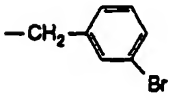
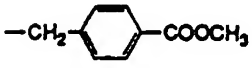
Compound No.	$-R^2$	$-R^1$
1	$-CH_3$	$-(CH_2)_3CH_3$
2	"	
5	$-C_2H_5$	"
6	$-CH(CH_3)_2$	"
7	$-CH_2$ 	"

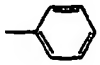
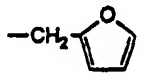
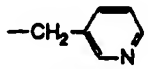
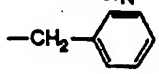
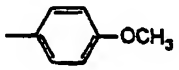
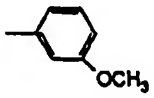
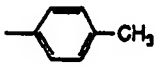
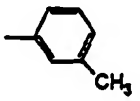
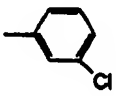
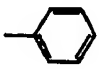
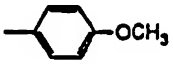
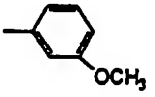
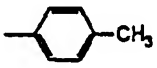
Table1-2

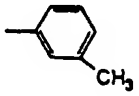
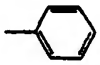


Compound No.	—R³	—R²	—R¹
3	—H	—H	
4	"	—CH_3	"
8	"	—C_2H_5	"
9	"	—$(CH_2)_2CH_3$	"
10	"	—$CH(CH_3)_2$	"
11	"	—$(CH_2)_3CH_3$	"
12	"	—$CH_2CH(CH_3)_2$	"
13	"	—CH_2— 	"
14	"	—CH_2COCH_3	"
15	"	—CH_2CH_2— 	"
16	"	—CH()—CH_3	"
17	"	—CH_2COOH	"
18	—CH_3	—H	"
19		"	"
20	—SH	"	"

Compound No.	$-R^3$	$-R^2$	$-R^1$
21	—OH	—H	
22	—H	"	
23	"	"	
24	"	"	
25	"	"	
26	"	"	
27	"	"	—$(CH_2)_3CH_3$
28	"	—CH_3	"
29	"	—$(CH_2)_2CH_3$	"
30	"	—$(CH_2)_5CH_3$	
31	"	—$CH_2CH_2OCH_2CH_3$	"
32	"	—$CH_2COOCH_2CH_3$	"
33	"	—$CH_2CH=CH_2$	"
34	"	—$CH_2CH_2OCOCH_3$	"
35	"	—CH $(CH_2CH_2CH_3)_2$	"
36	"	—$CH_2CH=CH$— 	"
37	"	—CH_2— 	"
38	"	—CH 	"

Compound No.	$-R^3$	$-R^2$	$-R^1$
39	—H		
40	"		"
41	"		"
42	"		"
43	"		"
44	"		"
45	"		"
46	"		"
47	"		"
48	"		"
49	"		"
50	"		"
51	"	—$(CH_2)_2CH_2OH$	"

Compound No.	$-R^3$	$-R^2$	$-R^1$
52	—H	$-CH_2CH(OH)CH_3$	
53	"		"
54	"		"
55	"		
56	"	"	
57	"	"	
58	"	"	
59	"	"	
60	$-CH_3$	"	
61		"	"
62	—H	$-CH_2CH(CH_3)_2$	
63	"	"	
64	"	"	

Compound No.	$-R^3$	$-R^2$	$-R^1$
65	$-H$	$-CH_2CH(CH_3)_2$	
66	"	$-(CH_2)_2CH_2-N$ O	
67	"	$-(CH_2)_2CH_2N(CH_2CH_3)_2$	"
68	"	$-CH_2CH_2CH_2Cl$	"
69	"	$-CH_2CH_2CH_2I$	"

The pharmacological activities of Compounds (I) are illustrated below.

a) Effect on carrageenin-induced paw edema

Male Wistar rats weighing 150 to 160 g (n =3 - 5) were used in the experiment. After the right hind paw volume was measured with the plethysmograph (TK-101; Unicom Co., Ltd.), the test compound (25, 50 or 100 mg/kg) was orally administered. After one hour, 0.1 ml of 1% carrageenin (λ-carrageenin; PICNIN-A®, Zushi Kagaku Co:, Ltd.) was subcutaneously injected into the right hind paw footpad. Three hours after the injection of carrageenin, the right hind paw volume was measured and the swelling rate was determined by the following equation 1.

$$\text{Swelling rate (\%)} = \frac{Vt - Vo}{Vo} \times 100 \quad (1)$$

Vt : the right hind paw volume measured 3 hours after the injection of carrageenin
Vo : the right hind paw volume measured prior to the injection of carrageenin

The suppression rate was calculated by the following equation 2.

$$\text{Suppression rate (\%)} = \frac{Swc - Swt}{Swc} \times 100 \quad (2)$$

Swt : the swelling rate of the group administered with the test compound
Swc : the swelling rate of the control group administered with physiological saline solution

The results are shown in Table 2.

b) Effect on zymosan-induced paw edema

The experiment was carried out in the same manner as in the carrageenin-induced paw edema test except that 1% zymosan (Zymosan A®; Sigma Chemical Co.) was used in place of 1% carrageenin and the right hind paw volume was measured 4 hours after the injection of the edema-inducing substance instead of 3 hours. The swelling rate and the suppression rate were calculated by equation 1 and equation 2, respectively. The results are shown in Table 2.

Table 2

Compound	Suppression rate for paw swelling (%)	
	(a) Carrageenin -induced edema	(b) Zymosan -induced edema
1	40.1	38.8
5	20.6	-
6	22.0	-
8	56.1	64.9
9	52.4	61.2 [a]
10	43.1	53.0
11	56.4	55.5 [a]
12	48.5	69.7 [a]
13	58.1	65.1
14	44.0	53.7 [a]
15	5.2	25.7 [a]
16	3.5	N. T
17	10.8	N. T

Compound	Suppression rate for paw swelling (%)	
	(a) Carrageenin -induced edema	(b) Zymosan -induced edema
18	23.7	26.7 [a]
19	1.7	N. T
20	6.8	N. T
21	2.3	N. T
22	1.9	0
23	0	18.1 [a]
24	0.3 [b]	N. T
25	13.8	N. T
26	15.2	N. T
27	8.6	N. T
28	20.6	26.7 [a]
29	56.1	21.1 [a]
30	48.5	33.5 [a]
31	60.6	57.4 [a]
33	67.8 [b]	67.3 [a]
34	42.2 [b]	41.6 [a]
37	34.7 [b]	49.8 [a]
40	21.3	42.8 [a]
41	47.7	33.3 [a]
42	35.9	45.6 [a]
43	39.2	56.2 [a]
44	42.8	63.9 [a]

Compound	Suppression rate for paw swelling (%)	
	(a) Carrageenin -induced edema	(b) Zymosan -induced edema
45	37.8	66.9 [a]
46	N. T	43.5 [a]
47	33.1	35.7 [a]
58	36.3 [b]	47.0 [a]
59	36.4 [b]	47.9 [a]

a: 25 mg/kg P.O. b: 50 mg/kg P.O.

c) Effect on Type III allergic reaction-induced pleurisy

1. Preparation of IgG fraction of rabbit anti-egg white albumin (anti-OA)

IgG was purified from rabbit anti-OA serum prepared in advance by the method of Koda et al. [Folia Pharmacol., Japon 66, 237, (1970)] in the following manner.

A saturated solution of ammonium sulfate (half volume of the serum) was added to the anti-OA serum, and the mixture was left for one hour at 4°C. The precipitate was taken by centrifugation (3,000 rpm, 30 min. 4°C) and dissolved in phosphate buffer of Dulbecco. Then, ammonium sulfate fractionation was carried out three times in the same manner as above, whereby a purified IgG fraction was obtained.

2. Type III allergic reaction-induced pleurisy

Male Wistar rats weighing 225 - 250 g were pre-bred for several days and fasted overnight prior to the experiment. The test compound (100 mg/kg) was orally administered to the animals, and after 30 minutes, a solution of IgG of rabbit anti-OA (0.2 ml, 5 mg protein/ml) was injected into the pleural cavity of the animals from the right side of thorax under anesthesia with ether. Thirty minutes after the injection of IgG, OA (albumin egg grade III; Sigma Chemical Co.) was intravenously injected into the animals as an inducer of pleurisy. After two hours, Evans Blue (25 mg/kg) was intravenously injected, and four and a half flours after the induction of pleurisy, the animals were killed by bleeding.

Then, an exudate in the pleural cavity was obtained, and the volume of the exudate was measured. The pleural cavity was rinsed with 5 ml of physiological saline and the rinsings were added to the exudate. The number of infiltrated cells in the mixture was counted and the volume of the dye in the mixture was determined by the absorption at 625 nm [Agent Actions., 25, 326 (1988)]. The suppression rates for the volume of the exudate, the number of infiltrated cells and the volume of the dye in the pleural cavity were calculated by the following equation 3.

$$\text{Suppression rate (\%)} = 100 - \frac{S.V - N.V}{P.V - N.V} \times 100 \qquad (3)$$

S.V : the value obtained with the group administered with the test compound and in which pleurisy is induced
N.V : the value obtained with the group in which pleurisy is not induced
P.V : the value obtained with the group administered with no test compound and in which pleurisy is induced

The results are shown in Table 3.

Table 3

Compound	Suppression rate (%)		
	Volume of exudate	Volume of dye in the exudate	Number of infiltrated cells in the exudate
1	100	80.3	84.1

d) Effect on passive Schultz-Dale reaction (broncho-dilative activity)

Male Hartley guinea pigs weighing 350 to 500 g were passively sensitized by intraperitoneal injection of rabbit anti-OA serum prepared in advance by the method of Koda et al. [Folia Pharmacol., Japon 66, 237, (1970)]. After 24 hours, the guinea pigs were stunned and exsanguinated, and then tracheae were removed. The zig-zag strips of the tracheae were prepared by the method of Emmerson and Mackay [J. Pharm. Pharmacol., 31, 798, (1979)]. The strips were suspended in Krebs-Henseleit solution at 37°C under aeration of a mixed gas of 95% oxygen and 5% carbon dioxide, and equilibrated for one hour. Then, antigen (egg white albumin) was introduced in the solution (final concentration; 1 µg/ml), and the contraction was measured by isotonictransducer (TD-112s, made by Nihon Kohden K.K., Japan) and recorded on a recorder (Type 3066, made by Yokogawa-Hokushin Denki, K.K. Japan). After the contraction curves reached a plateau, the test compounds were successively added in order to get cumulative concentration-relaxation curves. The concentration of 50% relaxation rate (IC_{50}) was calculated from the regression line, which was obtained from the cumulative concentration-relaxation curves.

The results are shown in Table 4.

Table 4

Compound	Passive Schultz-Dale reaction (IC_{50}; µM)
1	12
3	0.77
4	0.24
5	> 10
6	> 10
7	> 10
8	0.45
9	6.5
10	6.0
11	> 10
12	8.5
13	1.3
14	5.8
15	8.1
16	> 10
17	> 10
18	> 10

Compound	Passive Schultz-Dale reaction (IC_{50}; μM)
19	> 10
20	> 10
21	2.0
22	> 10
23	> 10
24	> 10
25	> 10
26	> 10
27	> 10
28	4.5
29	0.29
31	0.13
32	0.68
33	0.0071
34	0.68
37	6.2
41	10
44	6.6
48	4.9

e) Inhibition effect on platelet activating factor (PAF)-induced mortality

The experiment was carried out by a minor modification of a known method [Br. J. Pharmacol., 79, 595 (1983)]. Groups each consisting of 10 male dd mice (weighing 28 to 32 g) were used, and 50 or 100 mg/kg of the test compound or a saline (control) was orally administered. One hour after the administration of test compound, 40 μg/kg of PAF (manufactured by Avanti Polar Lipids Co., Ltd.) was intravenously administered. Three hours after PAF injection, the mortality of the animals was observed. The compound whose mortality was significantly (Fischer's accurate probability tests) lower than control is regarded as having inhibitory effect on PAF-induced mortality, and the results are shown in Table 5 as survival rate.

Table 5

Compound	Survival rate of control group	Survival rate of test compound-administered group
1	20 %	90 % ***
3	0 %	70 % **
5	0 %	80 % ***
6	10 %	70 % **
7	20 %	90 % **
8	0 %	70 % **
9	0 %	100 % ***
10	0 %	80 % ***
11	0 %	100 % ***
12	0 %	100 % ***

Compound	Survival rate of control group	Survival rate of test compound-administered group
13	10 %	90 % ***
14	0 %	100 % ***
15	10 %	50 %
16	0 %	0 %
17	0 %	30 %
18	10 %	90 % ***
19	10 %	60 %
20	10 %	30 %
21	10 %	30 %
22	0 %	30 %
23	0 %	10 %
24	10 %	40 %
25	10 %	60 %
26	10 %	90 % ***
27	0 %	60 % **
28	0 %	70 % **
29	0 %	100 % ***
30	0 %	90 % ***
31	0 %	90 % ***
32	0 %	0 %
33	0 %	100 % ***
34	0 %	70 % **
35	10 %	70 % **

Compound	Survival rate of control group	Survival rate of test compound-administered group
36	10 %	20 %
37	10 %	90 % ***
38	10 %	30 %
39	0 %	0 %
40	0 %	40 %
41	0 %	80 % ***a
42	0 %	100 % ***a
43	0 %	70 % **
44	0 %	50 %
45	0 %	40 %
46	0 %	10 %
47	0 %	0 %
48	0 %	10 %
49	0 %	0 %
50	0 %	0 %
51	0 %	80 % ***
52	0 %	100 % ***
53	0 %	90 % ***
54	0 %	90 % ***
55	0 %	0 %
56	10 %	40 %
57	0 %	0 %
58	0 %	100 % ***

Compound	Survival rate of control group	Survival rate of test compound-administered group
59	10 %	70 % **
60	0 %	20 %
61	0 %	10 %
62	10 %	90 % ***
64	10 %	60 %
66 Sa	0 %	70 % **
67 Sa	10 %	30 %

a : 50 mg/kg p.o.

** : $p < 0.01$, *** : $p < 0.001$ $n = 10$

Sa : hydrochloride of the compound

f) Acute toxicity

The test compound was orally and intraperitoneally administered to ddY strain male mice weighing 20 to 25 g. MLD (Minimum Lethal Dose) was determined by observing the mortality for days after the administration.

The results are shown in Table 6.

Table 6

Compound	M L D (mg/kg)	
	p.o.	i.p.
2	> 300	> 100
3	> 300	> 100
4	> 50	> 50
8	> 50	> 50
9	> 100	> 100
10	> 100	> 100
11	> 200	> 100
12	> 200	> 50
13	> 300	> 100
14	> 100	> 100
15	> 300	> 100
16	> 300	> 100
17	> 300	> 100
21	> 300	> 100
29	> 100	> 100
30	> 300	> 100
31	> 300	> 100
32	> 300	> 100
33	> 300	> 100
34	> 300	> 100
35	> 300	> 100
36	> 300	> 100

Compound	M L D (mg/kg)	
	p.o.	i.p.
43	> 300	> 100
44	> 300	> 50
47	> 300	> 100
58	> 300	> 100
59	> 300	> 100
66 Sa	> 300	> 100
67 Sa	> 300	> 100

Sa : hydrochloride of the compound

Compounds (I) and pharmaceutically acceptable salts thereof may be used as they are or in various preparation forms. The pharmaceutical composition of the present invention can be prepared by uniformly mixing Compound (I) or a pharmaceutically acceptable salt thereof as the active ingredient in an effective amount, with pharmaceutically acceptable carriers. These pharmaceutical compositions are desirably in a single dose unit which is suited for oral or parenteral administration.

In preparing the composition for oral administration, any pharmaceutically acceptable carriers may be used according to the preparation form. For example, liquid preparations such as a suspension and a syrup may be prepared using water; sugars such as sucrose, sorbitol and fructose; glycols such as polyethylene glycol and propylene glycol; oils such as sesame oil, olive oil and soybean oil; preservatives such as p-hydroxybenzoic acid esters; flavors such as strawberry flavor and peppermint, etc. Powders, pills, capsules and tablets may be prepared using excipients such as lactose, glucose, sucrose and mannitol; disintegrators such as starch and sodium alginate; lubricants such as magnesium stearate and talc; binders such as polyvinyl alcohol, hydroxypropyl cellulose and gelatin; surfactants such as fatty acid esters; plasticizers such as glycerine, etc. Tablets and capsules are the most useful single dose units for oral administration since their administration is easy. In preparing tablets and capsules, solid pharmaceutical carriers are used.

A solution for parenteral administration may be prepared using carriers such as distilled water, a saline solution, a glucose solution, and a mixture of a saline solution and a glucose solution.

The effective dose and the administration schedule of Compounds (I) or pharmaceutically acceptable salts thereof vary depending upon mode of administration, age, body weight and conditions of a patient, etc., but it is generally preferred to administer the effective compound in a dose of 1 to 1,000 mg/person/day at one time or in 2 to 4 parts.

Furthermore, Compounds (I) may be administered by inhalation in the form of aerosol, finely pulverized powders, or spray solution. In the case of aerosol administration, the present compounds are dissolved in an appropriate pharmaceutically acceptable solvent, for example, ethyl alcohol or a combination of miscible solvents, and then mixed with a pharmaceutically acceptable propellant.

Certain embodiments of the present invention are illustrated in the following examples.

Example 1

5-(n-Butyl)-1-methyl-1H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 1)

In 100 ml of ethanol was suspended 2.0 g (7.7 mmol) of Compound e obtained in Reference Example 5, and 0.40 g of 10% palladium/carbon was added to the suspension. Hydrogen gas was bubbled into the mixture at room temperature for 2 hours. After the catalyst was removed by filtration, the solvent was distilled off under reduced pressure.

To the resulting residue was added 12.8 ml (77.5 mmol) of ethyl orthoformate, and the mixture was stirred at 130°C for 30 minutes. The resulting solution was cooled to room temperature and filtered to obtain crystals. Recrystallization from isopropanol-isopropyl ether gave 1.0 g (yield 51%) of Compound 1 as white crystals.

Melting point: 198.5 -202°C

Elemental analysis (%): $C_{14}H_{16}N_4O$			
Calcd.:	C 65.61,	H 6.29,	N 21.86
Found :	C 65.50,	H 6.49,	N 22.09

IR(KBr) vmax(cm^{-1}): 1665, 1547, 1379

^{1}H-NMR($CDCl_3$) δ (ppm): 8.58(1H, dd, J=4, 2Hz), 8.26 (1H, dd, J=8, 2Hz), 7.76(1H, s) , 7.22 (1H, dd, J= 8, 4Hz), 4.60(2H, t, J=7Hz), 4.16(3H, s), 1.65-1.80(2H, m), 1.37-1.53(2H, m), 0.95(3H, t, J=7Hz)

MS m/e: 256(M^+), 214, 200

Example 2

1-Methyl-5-phenyl-1H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 2)

Compound b obtained in Reference Example 2 (1.2 g, 4.0 mmol) was suspended in a solvent mixture of 10 ml of ethanol and 10 ml of water, and 2.8 g (16 mmol) of sodium hydrosulfite was added to the suspension. After stirring in an oil bath at 100°C for 10 minutes, the resulting solution was cooled and then filtered. The obtained crystals were washed with water and dried, followed by addition of 8.0 ml (48 mmol) of ethyl orthoformate. The mixture was stirred at 130°C for one hour. The resulting solution was cooled and 30 ml of isopropyl ether was added thereto. Crude crystals were collected by filtration. Recrystalllization from isopropanol-isopropyl ether gave 0.64 g (yield 58%) of Compound 2 as white crystals.

Melting point: 262°C (carbonized)

Elemental analysis (%): $C_{16}H_{12}N_4O$			
Calcd.:	C 69.55,	H 4.38,	N 20.28
Found :	C 69.68,	H 4.27,	N 20.19

IR(KBr) vmax(cm^{-1}): 1667, 1575, 1550

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.60 (1H, dd, J=8, 2Hz), 8.35 (1H, dd, J=4, 2Hz), 8.20 (1H, s), 7.41-7.57(3H, m), 7.34 (1H, dd, J=8, 4Hz), 7.22-7.27(2H, m), 4.22 (3H, s)

MS m/e: 276(M^+), 275

Example 3

5-Phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 3)

Compound 3 was obtained as colorless crystals (yield 58%) according to the same procedure as in Example 2 except that Compound c obtained in Reference Example 3 was used instead of Compound b and the recrystallization was carried out from dimethylformamide-water.

Melting point: >300°C

Elemental analysis (%): $C_{15}H_{10}N_4O$-0.2H_2O			
Calcd.:	C 67.76,	H 3.94,	N 21.07
Found :	C 67.92,	H 3.45,	N 21.10

IR(KBr) vmax(cm^{-1}): 1668, 1583, 1423

^{1}H-NMR(d_6-DMSO) δ (ppm): 13.84 (1H, br.s), 8.50 (1H, dd, J=8, 2Hz), 8.33-8.36(2H, m), 7.42-7.58(3H, m), 7.22-7.38 (3H, m)

MS m/e: 262(M^+), 261

Example 4

3-Methyl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 4)

In 30 ml of dimethylformamide was dissolved 0.80 g (3.1 mmol) of Compound 3 obtained in Example 3, and 0.18 g (4.6 mmol) of 60% sodium hydride in oil was added to the solution at room temperature. After evolution of hydrogen ceased, 0.40 ml (6.3 mmol) of methyl iodide was added to the reaction mixture, followed by stirring for 5 hours. Then, 2 ml of a saturated aqueous solution of ammonium chloride was added to the mixture, and the solvent was distilled off under reduced pressure. The resulting residue was subjected to silica gel column chromatography (developing solvent: chloroform/methanol = 70/1) to obtain crystals. Recrystallization from ethanol-isopropyl ether gave 0.61 g (yield 72%) of Compound 4 as colorless crystals.

Melting point: >300°C

Elemental analysis (%): $C_{16}H_{12}N_4O$			
Calcd.:	C 69.55,	H 4.38,	N 20.28
Found :	C 69.85,	H 4.10,	N 20.28

IR(KBr) vmax(cm^{-1}): 1663, 1574

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.50(1H, dd, J=8, 2Hz), 8.34 (1H, s), 8.34(1H, dd, J=4, 2Hz), 7.42-7.57 (3H, m), 7.27-7.36 (3H, m), 4.06(3H, s)

MS m/e: 276(M^+), 275

Example 5

1-Ethyl-5-phenyl-1H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 5)

Compound 5 was obtained according to the same procedure as in Example 3 except that Compound h obtained in Reference Example 6 was used instead of Compound c (yield 24%).

Melting point (solvent for recrystallization): >300°C (methanol)

Elemental analysis (%): $C_{17}H_{14}N_4O$			
Calcd.:	C 70.33,	H 4.81,	N 19.33
Found :	C 70.33,	H 4.86,	N 19.30

IR(KBr) vmax(cm^{-1}): 1666, 1378, 712

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.52(1H, dd, J=8, 2Hz), 8.36 (1H, dd, J=4, 2Hz), 8.27(1H, s), 7.40-7.60(4H, m), 7.37(1H, dd, J=8, 4Hz), 7.21-7.29(2H, m), 4.67 (2H, q, J=7Hz), 1.51(3H, t, J=7Hz)

MS m/e: 290(M^+), 289

Example 6

1-Isopropyl-5-phenyl-1H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 6)

Compound 6 was obtained according to the same procedure as in Example 3 except that Compound i obtained in Reference Example 7 was used instead of Compound c (yield 56%).

Melting point (solvent for recrystallization): >300°C (ethanol)

Elemental analysis (%): $C_{18}H_{16}N_4O$			
Calcd.:	C 71.02,	H 5.23,	N 18.16

(continued)

Elemental analysis (%): $C_{18}H_{16}N_4O$			
Found :	C 71.04,	H 5.30,	N 18.41

IR(KBr) vmax(cm^{-1}): 1664

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.58 (1H, dd, J=8, 2Hz), 8.44 (1H, s), 8.35(1H, dd, J=4, 2Hz), 7.41-7.57(4H, m), 7.36(1H, dd, J=8, 4Hz), 7.22-7.28 (2H, m)

MS m/e: 304(M^+), 303, 261

Example 7

1-Benzyl-5-phenyl-1H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 7)

Compound 7 was obtained according to the same procedure as in Example 3 except that Compound j obtained in Reference Example 8 was used instead of Compound c (yield 15%).

Melting point (solvent for recrystallization): >300°C (ethanol)

Elemental analysis (%): $C_{22}H_{16}N_4O$			
Calcd.:	C 74.59,	H 4.58,	N 16.20
Found :	C 74.98,	H 4.58,	N 15.90

IR(KBr) vmax(cm^{-1}): 1661

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.42(1H, s), 8.27(1H, dd, J= 4, 2Hz), 8.24(1H, dd, J=8, 2Hz), 7.15-7.57(11H, m), 5.95(2H, s)

MS m/e: 352(M^+), 351, 91

In Examples 8 -16, the same procedure as in Example 4 was repeated except that the compounds shown in Table 7 were used respectively instead of methyl iodide.

Example 8

3-Ethyl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 8)

Melting point (solvent for recrystallization): 233 -234°C (chloroform-isopropyl ether)

Elemental analysis (%): $C_{17}H_{14}N_4O$			
Calcd.:	C 70.58,	H 4.82,	N 19.50
Found :	C 70.33,	H 4.86,	N 19.29

IR(KBr) vmax(cm^{-1}): 1661

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.53(1H, dd, J=8, 2Hz), 8.43 (1H, s), 8.36(1H, dd, J=4, 2Hz), 7.27-7.58(6H, m), 4.50(2H, q, J=7Hz), 1.44(3H, t, J=7Hz)

MS m/e: 290(M^+), 289

Example 9

5-Phenyl-3-n-propyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 9)

Melting point (solvent for recrystallization): 194 -204°C (ethyl acetate-n-hexane)

Elemental analysis (%): $C_{18}H_{16}N_4O$			
Calcd.:	C 71.10,	H 5.37,	N 18.75
Found :	C 71.03,	H 5.30,	N 18.41

IR(KBr) vmax(cm^{-1}): 1661, 457

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.52(1H, dd, J=8, 2Hz), 8.42 (1H, s), 8.36(1H, dd, J=4, 2Hz), 7.23-7.65(6H, m), 4.41(2H, t, J=7Hz), 1.73-1.93(2H, m), 0.86(3H, t, J=7Hz)

MS m/e: 304(M^+), 303, 261

Example 10

3-Isopropyl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 10)

Melting point (solvent for recrystallization): 192 - 193°C (isopropanol-water)

Elemental analysis (%): $C_{18}H_{16}N_4O$			
Calcd.:	C 71.07,	H 5.17,	N 18.33
Found :	C 71.03,	H 5.30,	N 18.41

IR(KBr) vmax(cm^{-1}): 1661, 732

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.57(1H, s), 8.55(1H, dd, J=8, 2Hz), 8.36(1H, dd, J=4, 2Hz), 7.43-7.60(3H, m), 7.26-7.39(3H, m), 5.25-5.41(1H, m), 1.56(6H, d)

MS m/e: 304(M^+), 303, 261

Example 11

3-n-Butyl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 11)

Melting point (solvent for recrystallization): 192 -194°C (ethyl acetate-isopropyl ether)

Elemental analysis (%): $C_{19}H_{18}N_4O$			
Calcd.:	C 71.55,	H 5.73,	N 17.67
Found :	C 71.68,	H 5.70,	N 17.60

IR(KBr) vmax(cm^{-1}): 1667, 717

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.52(1H, dd, J=8, 2Hz), 8.42 (1H, s), 8.36(1H, dd, J=4, 2Hz), 7.42-7.58(3H, m), 7.25-7.39(3H, m), 4.45(2H, t, J=7Hz), 1.72-1.89 (2H, m), 1.21-1.39(2H, m), 0.89(3H, t, J=7Hz)

MS m/e: 318(M^+), 317, 261

Example 12

3-Isobutyl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 12)

Melting point (solvent for recrystallization): 255 - 267°C (isopropyl ether)

Elemental analysis (%): $C_{19}H_{18}N_4O$-0.1H_2O			
Calcd. :	C 71.15,	H 5.62,	N 17.46
Found :	C 71.28,	H 5.73,	N 14.50

IR(KBr) vmax(cm^{-1}): 1671

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.53(1H, dd, J=8, 2Hz), 8.40 (1H, s), 8.36(1H, dd, J=4, 2Hz), 7.26-7.60(6H, m), 4.26(2H, d, J=7Hz), 2.10-2.25(1H, m), 0.86(6H, d, J=7Hz)

MS m/e: 318(M^+), 317, 262

Example 13

3-Benzyl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 13)

Melting point (solvent for recrystallization): 188 - 192°C (ethanol-water)

Elemental analysis (%): $C_{22}H_{16}N_4O$			
Calcd.:	C 75.13,	H 4.57,	N 15.97
Found :	C 74.98,	H 4.57,	N 15.59

IR(KBr) vmax(cm^{-1}): 1668, 1651

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.59(1H, s), 8.53(1H, dd, J= 8, 2Hz), 8.36(1H, dd, J=4, 2Hz), 7.26-7.60(11H, m), 5.72(2H, s)

MS m/e: 352(M^+), 351, 91

Example 14

3-(2-Oxopropyl)-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 14)

Melting point (solvent for recrystallization): 275 -276°C (ethyl acetate)

Elemental analysis (%): $C_{18}H_{14}N_4O_2$			
Calcd.:	C 67.75,	H 4.23,	N 17.38
Found :	C 67.91,	H 4.43,	N 17.59

IR(KBr) vmax(cm^{-1}): 1661

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.62(1H, dd, J=8, 2Hz), 8.45 (1H, dd, J=4, 2Hz), 7.90(1H, s), 7.47-7.65(3H, m), 7.25-7.35(3H, m), 5.38(2H, s), 2.32 (3H, s)

MS m/e: 318(M^+), 317, 275

Example 15

3-Phenethyl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 15)

Melting point (solvent for recrystallization): 232 - 233°C (isopropanol-ethanol-water)

Elemental analysis (%): $C_{23}H_{18}N_4O$			
Calcd.:	C 75.42,	H 4.92,	N 15.15
Found :	C 75.39,	H 4.95,	N 15.29

IR(KBr) vmax(cm^{-1}): 1650

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.58(1H, dd, J=8, 2Hz), 8.45 (1H, dd, J=4, 2Hz), 7.48-7.72 (4H, m), 7.06-7.47 (8H, m), 4.72(2H, t, J=7Hz), 3.21(2H, t, J=7Hz)

MS m/e: 366(M^+), 261

Example 16

3-(α-Methyl)benzyl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 16)

Melting point (solvent for recrystallization): 221 - 226°C (chloroform-isopropyl ether)

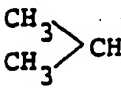
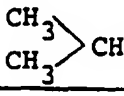
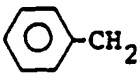
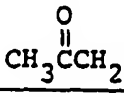
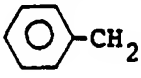
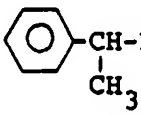
Elemental analysis (%): $C_{23}H_{18}N_4O$			
Calcd.:	C 75.14,	H 5.21,	N 15.04
Found :	C 75.39,	H 4.95,	N 15.29

IR(KBr) νmax(cm^{-1}): 1661

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.55(1H, dd, J=8, 2Hz), 8.29-8.42(2H, m), 7.16-7.62(6H, m), 5.27(2H, s)

MS m/e: 360(M^+), 261

Table 7

Compound	Compound used instead of methyl iodide	Yield (%)
8	CH_3CH_2I	96
9	$CH_3CH_2CH_2I$	71
10		41
11	$CH_3CH_2CH_2CH_2I$	70
12		71
13		78
14		60
15		75
16		75

Example 17

3-Carboxymethyl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 17)

The same procedure as in Example 4 was repeated except that tert-butyl bromoacetate was used instead of methyl iodide, whereby 3-tert-butyloxycarbonylmethyl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 101) was obtained (yield 55%).

Compound 101 (3.6 g) was dissolved in 180 ml of methylene chloride, and 80 ml of trifluoroacetic acid was added to the solution under ice cooling. The mixture was stirred at room temperature for 6 hours, and the solvent was distilled off under reduced pressure. The resulting residue was suspended in water and 4N aqueous solution of sodium hydroxide was added to dissolve the residue. Thereafter 2N hydrochloric acid was added to the solution to give the precipitate, which was collected by filtration. Recrystallization from dimethylformamide (hereinafter referred to as DMF)-water gave 1.4 g (yield 45%) of Compound 17 as white crystals.

Melting point (solvent for recrystallization): >300°C (DMF-water)

Elemental analysis (%): $C_{17}H_{12}N_4O_3$			
Calcd.:	C 63.71,	H 3.71,	N 17.69
Found :	C 63.74,	H 3.77,	N 17.49

IR(KBr) νmax(cm^{-1}): 1722, 1709, 1687, 1662

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.62(1H, dd, J=8, 2Hz), 8.44 (1H, dd, J=4, 2Hz), 8.00(1H, s), 7,17-7.70(11H, m), 6.70(1H, q, J=7Hz), 1.98(3H, d, J=7Hz)

MS m/e: 320(M^+), 319, 275

Example 13

2-Methyl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 18)

Compound c obtained in Reference Example 3 (12 g, 43 mmol) was suspended in 10 ml of ethanol and 14 ml of water, and 30 g (170 mmol) of sodium hydrosulfite was added to the suspension. After stirring in an oil bath at 100°C for 10 minutes, the resulting solution was cooled and then filtered. The resulting crystals were dried to give 9.4 g (yield 88%) of 3,4-diamino-1-phenyl-1,8-naphthyridin-2(1H)-one (Compound 102) as a crude product.

Compound 102 (4.0 g, 16 mmol) was then suspended in 100 ml of methylene chloride, and 3.1 ml (22 mmol) of triethylamine and 1.4 ml (19 mmol) of acetyl chloride were successively added to the suspension under ice cooling with stirring. The mixture was stirred at room temperature for 1.5 hours.

Then, methanol was added to the mixture and the solvent was distilled off under reduced pressure. To the resulting residue were added 10 ml of dioxane and 10 ml of 2N sodium hydroxide solution, and the mixture was refluxed for 1.5 hours. The mixture was cooled with ice, and conc. hydrochloric acid was added thereto for neutralization. The formed crystals were taken by filtration. Recrystallization from methanol gave 2.0 g (yield 45%) of Compound 18 as colorless crystals.

Melting point (solvent for recrystallization): >300°C (methanol)

Elemental analysis (%): $C_{16}H_{12}N_4O$-0.5H_2O			
Calcd.:	C 67.53,	H 4.32,	N 19.47
Found :	C 67.36,	H 4.59,	N 19.63

IR(KBr) νmax(cm^{-1}): 1657, 730

^{1}H-NMR(d_6-DMSO) δ (ppm): 13.5(1H, br.s), 8.57(1H, dd, J=8, 2Hz), 8.33(1H, dd, J=4, 2Hz), 7.18-7.61(6H, m), 2.51(3H, s)

MS m/e: 276(M^+), 275

Example 19

2,5-Diphenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 19)

Compound 19 was obtained as colorless crystals according to the same procedure as in Example 18 except that benzoyl chloride was used instead of acetyl chloride (yield 73%).

Melting point (solvent for recrystallization): >300°C (chloroform)

Elemental analysis (%): $C_{21}H_{14}N_4O$			
Calcd.:	C 74.50,	H 4.05,	N 16.49
Found :	C 74.54,	H 4.17,	N 16.56

IR(KBr) vmax(cm^{-1}): 1651, 457
^{1}H-NMR(d_6-DMSO) δ (ppm): 8.29-8.41(3H, m) , 7.27-7.72 (10H, m)
MS m/e: 338(M^+) , 337

Example 20

2-Mercapto-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 20)

Compound c obtained in Reference Example 3 (12 g, 43 mmol) was suspended in 10 ml of ethanol and 14 ml of water, and 30 g (170 mmol) of sodium hydrosulfite was added to the suspension. After stirring in an oil bath at 100°C for 10 minutes, the solution was cooled and the resulting precipitate was collected by filtration. The obtained crystals were dried to give 9.4 g (yield 88%) of 3,4-diamino-1-phenyl-1,8-naphthyridin-2(1H)-one (Compound 102) as a crude product.

Compound 102 (2.0 g, 7.9 mmol) was then suspended in 80 ml of tetrahydrofuran, and 2.3 g (13 mmol) of thioarbonyldiimidazole was added to the suspension. The mixture was heated to reflux for 2 hours. The solvent was distilled off under reduced pressure, and the residue was triturated with ethanol. The formed crystals were taken by filtration. Recrystallization from DMF gave 1.1 g (yield 47%) of Compound 20 as colorless crystals.

Melting point (solvent for recrystallization): >300°C (DMF)

Elemental analysis (%): $C_{15}H_{10}N_4OS$-0.1H_2O			
Calcd.:	C 60.74,	H 3.33,	N 19.14
Found :	C 60.84,	H 3.47,	N 18.92

IR(KBr) vmax(cm^{-1}): 1689, 1680
^{1}H-NMR(CF_3CO_2D) δ (ppm): 9.21(1H, dd, J=6, 1Hz), 8.62 (1H, dd, J=4, 1Hz), 8.02(1H, dd, J=6, 4Hz), 7.76-7.95(3H, m), 7.49-7.62(2H, m)
MS m/e: 294(M^+), 293, 44

Example 21

2-Hydroxy-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 21)

Compound 21 was obtained as colorless crystals according to the same procedure as in Example 20 except that carbonyldiimidazole was used instead of thiocarbonyldiimidazole (yield 45%).

Melting point (solvent for recrystallization): >300°C (DMF)

Elemental analysis (%): $C_{15}H_{10}N_4O_2$-0.7H_2O			
Calcd.:	C 61.72,	H 3.56,	N 19.18
Found :	C 61.93,	H 3.95,	N 19.26

IR(KBr) vmax(cm^{-1}): 1722, 1649, 1628

^{1}H-NMR(d_6-DMSO) δ (ppm): 9.27(1H, dd, J=6, 1Hz), 8.62 (1H, dd, J=4, 1Hz), 7.98(1H, dd, J=6, 4Hz), 7.76-7.95(3H, m), 7.47-7.63(2H, m)

MS m/e: 278(M^+), 277, 194

In Examples 22 -26, the same procedure as in Example 3 was repeated except that the compounds shown in Table 8 were used respectively instead of Compound c.

Example 22

5-(4-Methoxy)phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-(5)-one (Compound 22)

Melting point (solvent for recrystallization) : >300°C (DMF-water)

Elemental analysis (%): $C_{16}H_{12}N_4O_2$			
Calcd.:	C 65.64,	H 4.04,	N 19.25
Found :	C 65.75,	H 4.14,	N 19.17

IR(KBr) vmax(cm^{-1}) : 1668

Example 23

5-[3-Methoxy)phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-(5)-one (Compound 23)

Melting point (solvent for recrystallization): >300°C (DMF-water)

Elemental analysis (%): $C_{16}H_{12}N_4O_2$			
Calcd.:	C 65.70,	H 4.02,	N 19.32
Found :	C 65.75,	H 4.14,	N 19.17

IR(KBr) vmax(cm^{-1}) : 1667

Example 24

5-(4-Methyl)phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 24)

Melting point (solvent for recrystallization): >300°C (DMF-water)

Elemental analysis (%): $C_{16}H_{12}N_4O$			
Calcd.:	C 69.62,	H 4.16,	N 19.96
Found :	C 69.55,	H 4.38,	N 20.28

IR(KBr) vmax(cm^{-1}): 1665

Example 25

5-(3-Methyl)phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 25)

Melting point (solvent for recrystallization): >300°C (DMF-water)

Elemental analysis (%): $C_{16}H_{12}N_4O$			
Calcd.:	C 69.83,	H 4.58,	N 19.96
Found :	C 69.55,	H 4.38,	N 20.28

IR(KBr) νmax(cm^{-1}): 1667

Example 26

5-(3-Chloro)phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 26)

Melting point (solvent for recrystallization): >300°C (DMF-water)

Elemental analysis (%): $C_{15}H_9ClN_4O$			
Calcd.:	C 60.33,	H 2.81,	N 19.06
Found :	C 60.72,	H 3.06,	N 18.88

IR(KBr) νmax(cm^{-1}): 1668

Table 8

Compound	Starting Compound (Reference Example No.)	Yield (%)
22	n - 1 (20)	54
23	n - 2 (21)	50
24	n - 3 (22)	52
25	n - 4 (23)	37
26	n - 5 (24)	47

Example 27

5-n-Butyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 27)

Compound 27 was obtained according to the same procedure as in Example 3 except that Compound k obtained in Reference Example 9 was used instead of Compound c (yield 48%).

Melting point (solvent for recrystallization): >300°C (DMF-water)

Elemental analysis (%): $C_{13}H_{14}N_4O$			
Calcd.:	C 64.24,	H 5.80,	N 22.97
Found :	C 64.44,	H 5.82,	N 23.12

IR(KBr) νmax(cm) : 1664, 779

^{1}H-NMR(d_6-DMSO) δ (ppm) : 13.74(1H, br. s), 8.62(1H, dd, J=4, 2Hz), 8.51(1H, dd, J=8, 2Hz), 8.30(1H, br. s), 7.39(1H, dd, J=8, 4Hz), 4.52(2H, t, J= 7Hz), 1.53-1.76(2H, m), 1.27-1.48(2H, m), 0.93 (3H, t, J=7Hz)

MS m/e: 242(M^+), 200, 186

Example 28

5-n-Butyl-3-methyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 28)

Compound 28 was obtained according to the same procedure as in Example 4 except that Compound 27 obtained in Example 27 was used instead of Compound 3 (yield 72%).

Melting point (solvent for recrystallization): 173-174°C (isopropyl ether)

Elemental analysis (%): $C_{14}H_{16}N_4O$			
Calcd.:	C 65.22,	H 6.16,	N 21.89
Found :	C 65.61,	H 6.29,	N 21.86

IR(KBr) νmax(cm^{-1}): 1659, 776

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.50(1H, dd, J=4, 2Hz), 8.47 (1H, dd, J=8, 2Hz), 8.28(1H, s), 7.37(1H, dd, J=8, 4Hz), 4.49(2H, t, J=7Hz), 4.09(3H, s), 1.60-1.73(2H, m), 1.30-1.48(2H, m), 0.93(3H, t, J=7Hz)

MS m/e: 256(M^+), 199, 200

Example 29

5-n-Butyl-3-n-propyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 29)

Compound 29 was obtained according to the same procedure as in Example 28 except that n-propyl iodide was used instead of methyl iodide (yield 82%).

Melting point (solvent for recrystallization): 87-90°C (n-hexane)

Elemental analysis (%): $C_{16}H_{20}N_4O$			
Calcd.:	C 67.58,	H 7.16,	N 19.87
Found :	C 67.58,	H 7.09,	N 19.70

IR(KBr) νmax(cm^{-1}): 1661, 1369, 775

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.62(1H, dd, J=4, 2Hz), 8.50 (1H, dd, J=8, 2Hz), 8.35(1H, s), 7.37(1H, dd, J=8, 4Hz), 4.40-4.62(4H, m), 1.79-1.96(2H, m), 1.58-1.73(2H, m), 1.30-1.49(2H, m), 0.94(3H, t, J=7Hz), 0.88(3H, t, J=7Hz)

MS m/e: 284(M^+), 186

In Examples 30 -54, the same procedure as in Example 4 was repeated except that the compounds shown in Table 9 were used respectively instead of methyl iodide.

Example 30

3-Hexyl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 30)

Melting point (solvent for recrystallization): 166 -168°C (chloroform-isopropyl ether)

Elemental analysis (%): $C_{21}H_{22}N_4O$			
Calcd.:	C 72.85,	H 6.48,	N 16.32
Found :	C 72.80,	H 6.40,	N 16.17

IR(KBr) νmax(cm^{-1}): 1673, 1574

^{1}H-NMR ($CDCl_3$) δ (ppm): 8.61(1H, dd, J=8, 2Hz), 8.43 (1H, dd, J=4, 2Hz), 7.95(1H, s), 7.46-7.68(3H, m), 7.20-7.45(3H, m), 4.50(2H, t, J=7Hz),

1.80-2.11 (3H, m), 1.17-1.46(5H, m), 0.86(3H, t, J=7Hz)

MS m/e: 346(M^+), 345, 261

Example 31

3-(Ethoxyethyl)-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 31)

Meling point (solvent for recrystallization): 209 -210°C (chloroform-isopropyl ether)

Elemental analysis (%): $C_{19}H_{18}N_4O_2$			
Calcd.:	C 68.25,	H 5.43,	N 16.76
Found :	C 68.27,	H 5.35,	N 16.98

IR(KBr) vmax(cm^{-1}): 1661

^{1}H-NMR($CDCl_3$) δ (ppm): 8.63(1H, dd, J=8, 2Hz), 8.43 (1H, dd, J=4, 2Hz), 8.08(1H, s), 7.43-7.66(3H, m), 7.17-7.37(3H, m), 4.72(2H, t, J=5Hz), 3.79 (2H, t, J=5Hz), 3.46(2H, q, J=7Hz), 1.15(3H, t, J=7Hz)

MS m/e: 334(M^+), 305, 289, 261

Example 32

3-Ethoxycarbonylmethyl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 32)

Melting point (solvent for recrystallization): 228 -229°C (chloroform-isopropyl ether)

Elemental analysis (%): $C_{19}H_{16}N_4O_3$			
Calcd.:	C 65.50,	H 4.62,	N 16.08
Found :	C 64.97,	H 4.43,	N 16.10

IR(KBr) vmax(cm^{-1}): 1730, 1672, 1241

^{1}H-NMR($CDCl_3$) δ (ppm): 8.62(1H, dd, J=8, 2Hz), 8.44 (1H, dd, J=4, 2Hz), 8.00(1H, s), 7.46-7.65(3H, m), 7.18-7.38(5H, m), 5.33(2H, s), 4.25 (2H, q, J=7Hz), 1.27(3H, t, J=7Hz)

MS m/e: 348(M^+), 347

Example 33

3-(2-Propenyl)-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 33)

Melting point (solvent for recrystallization): 186 -189°C (chloroform-isopropyl ether)

Elemental analysis (%): $C_{18}H_{14}N_4O$			
Calcd.:	C 71.50,	H 4.66,	N 18.53
Found :	C 71.55,	H 4.68,	N 18.73

IR(KBr) vmax(cm^{-1}): 1665, 1573

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.53(1H, dd, J=8, 2Hz), 8.41 (1H, s), 8.36(1H, dd, J=4, 2Hz), 7.25-7.66(8H, m), 6.04-6.19(1H, m), 5.05-5.28(4H, m)

MS m/e: 302, 301(M^+)

Example 34

3-(2-Acetoxyethyl)-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 34)

Melting point (solvent for recrystallization): 198°C (ethyl acetate)

Elemental analysis (%): $C_{19}H_{16}N_4O_3$			
Calcd.:	C 65.51,	H 4.63,	N 16.88
Found :	C 65.03,	H 4.60,	N 16.18

IR(KBr) νmax(cm^{-1}): 1741, 1667

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.53(1H, dd, J=8, 2Hz), 8.43 (1H, s), 8.37(1H, dd, J=4, 2Hz), 7.25-7.60(6H, m), 4.71(2H, t, J=5Hz), 4.41(2H, t, J=5Hz), 1.95 (3H, s)

MS m/e: 348(M^+), 347, 261

Example 35

3-(1-Propylbutyl)-5-phenyl-3H-imidazo[4,5-c][1,8]-naphthyridin-4(5H)-one (Compound 35) .

Melting point (solvent for recrystallization): 104 -105°C (methanol-water)

IR(KBr) νmax(cm^{-1}): 2924, 1658

^{1}H-NMR($CDCl_3$) δ (ppm) : 8.62(1H, dd, J=8, 2Hz), 8.42 (1H, dd, J=4, 2Hz), 8.03(1H, s), 7.45-7.63(3H, m), 7.22-7.36(3H, m), 5.22-5.45(1H, m), 1.75-2.03 (4H, m), 1.10-1.42(4H, m), 0.89(6H, t, J=7Hz)

MS m/e: 360(M^+), 261

Example 36

3-Cinnamyl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 36)

Melting point (solvent for recrystallization): 231 - 233°C (chloroform-isopropyl ether)

Elemental analysis (%): $C_{24}H_{18}N_4O{\cdot}0.3H_2O$			
Calcd.:	C 75.10,	H 4.88,	N 14.60
Found :	C 75.23,	H 4.67,	N 14.56

IR(KBr) νmax(cm^{-1}): 1665, 1571

^{1}H-NMR(d_6-DMSO) δ (ppm) : 8.54(1H, dd, J=8, 2Hz), 8.48 (1H, s), 8.36(1H, dd, J=4, 2Hz), 7.20-7.58(11H, m), 7.50-7.67(2H, m), 7.25-7.33(2H, m)

MS m/e: 378, 117

Example 37

3-Cyclohexylmethyl-5-phenyl-3H-imidazo[4,5-c][1,8]-naphthyridin-4(5H)-one (Compound 37)

Melting point (solvent for recrystallization): 236°C (chloroform-n-hexane)

Elemental analysis (%): $C_{22}H_{22}N_4O$			
Calcd.:	C 73.71,	H 6.18,	N 15.63
Found :	C 73.55,	H 6.10,	N 15.64

IR(KBr) νmax(cm^{-1}) : 1678, 1573

^{1}H-NMR(d_6-DMSO) δ (ppm) : 8.51(1H, dd, J=8, 2Hz), 8.37 (1H, s), 8.35(1H, dd, J=4,

2Hz), 4.30(2H, d), 1.41-1.93(5H, m), 0.90-1.25(6H, m)

MS m/e: 358(M^+), 275, 261

Example 38

3-(3-Diphenylmethyl)-5-phenyl-3H-imidazo[4,5-c][1,8]-naphthyridin-4(5H)-one (Compound 38)

Melting point (solvent for recrystallization): 109 - 113°C (chloroform-isopropyl ether)

IR(KBr) vmax(cm^{-1}): 3652, 1674, 1495

^{1}H-NMR($CDCl_3$) δ (ppm): 8.61(1H, dd, J=8, 2Hz), 8.42 (1H, dd, J=4, 2Hz), 7.80(1H, s), 7.03-7.60(17H, m)

MS m/e: 428(M^+), 167

Example 39

3-(2,5-Dimethylphenyl)methyl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 39)

Melting point (solvent for recrystallization): 237-238°C (DMF-methanol)

Elemental analysis (%): $C_{24}H_{20}N_4O$			
Calcd.:	C 75.77,	H 5.30,	N 14.73
Found :	C 75.80,	H 5.28,	N 14.12

IR(KBr) vmax(cm^{-1}) : 1674

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.56(1H, dd, J=8, 2Hz), 8.35-8.42(2H, m), 7.24-7.53(6H, m), 6.96-7.12(4H, m), 6.61(1H, s), 5.71(2H, s), 2.28(3H, s), 2.16(3H, s)

MS m/e: 380(M^+) , 379

Example 40

3-(4-Chlorophenyl)methyl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 40)

Melting point (solvent for recrystallization): 287 -290°C (DMF-methanol)

Elemental analysis (%): $C_{22}H_{15}N_4OCl$			
Calcd.:	C 68.39,	H 3.91,	N 14.50
Found :	C 68.41,	H 3.62,	N 14.48

IR(KBr) vmax(cm^{-1}): 1671, 1616

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.61(1H, s), 8.52(1H, dd, J=8, 2Hz), 8.36(1H, dd, J=4, 2Hz), 7.23-7.58 (10H, m), 5.70(2H, s)

MS m/e: 388, 387, 386(M^+), 385

Example 41

3-(3-Methylphenyl)methyl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 41)

Melting point: (solvent for recrystallization): 238 -239°C (ethanol-methanol)

Elemental analysis (%): $C_{23}H_{18}N_4O$			
Calcd.:	C 75.39,	H 4.95,	N 15.29
Found :	C 75.17,	H 4.61,	N 15.28

IR(KBr) vmax(cm^{-1}): 1665, 1575

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.58(1H, s), 8.52(1H, dd, J=8, 2Hz), 8.36(1H, dd, J=4, 2Hz), 7.06-7.56 (10H, m), 5.68(2H, s), 2.26(3H, s)

MS m/e: 366(M^+), 365

Example 42

3-(4-Nitrophenyl)methyl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 42)

Melting point (solvent for recrystallization): 256 -259°C (DMF-methanol)

Elemental analysis (%): $C_{22}H_{15}N_5O_3$			
Calcd.:	C 63.61,	H 4.12,	N 16.86
Found :	C 63.76,	H 3.84,	N 16.28

IR(KBr) vmax(cm^{-1}): 1663, 1576

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.65(1H, s), 8.54(1H, dd, J= 8, 2H), 8.37(1H, dd, J=4, 2Hz), 8.19(2H, d, J= 9Hz), 7.17-7.61(8H, m), 5.85(2H, s)

MS m/e: 397(M^+), 396

Example 43

3-(4-Methylphenyl)methyl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 43)

Melting point (solvent for recrystallization): 238 -243°C (DMF-methanol)

Elemental analysis (%): $C_{23}H_{18}N_4O \cdot 0.8H_2O$			
Calcd.:	C 72.54,	H 5.19,	N 14.71
Found :	C 72.47,	H 5.05,	N 14.20

IR(KBr) vmax(cm^{-1}): 1669, 1575

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.57(1H, s), 8.51(1H, dd, J=8, 2Hz), 8.35(1H, dd, J=4, 2Hz), 7.05-7.58 (10H, m), 5.66(2H, s), 2.25(3H, s)

MS m/e: 366(M^+), 365, 105

Example 44

3-(4-Fluorophenyl)methyl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 44)

Melting point (solvent for recrystallization): 253 -256°C (DMF-methanol)

Elemental analysis (%): $C_{22}H_{15}N_4OF$			
Calcd.:	C 71.34,	H 4.08,	N 15.13
Found :	C 71.08,	H 3.68,	N 14.83

IR(KBr) vmax(cm^{-1}): 1667, 1511

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.61(1H, s), 8.51 (1H, dd, J= 8, 2Hz), 8.35(1H, dd, J=4, 2Hz), 7.12-7.58(10H, m), 5.69(2H, s)

MS m/e: 370(M^+), 369

Example 45

3-(4-Methoxyphenyl)methyl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 45)

Melting point (solvent for recrystallization): 267 -268°C (DMF-water)

Elemental analysis (%): $C_{23}H_{18}N_4O_2$			
Calcd.:	C 72.24,	H 4.74,	N 14.65
Found :	C 72.11,	H 4.32,	N 14.63

IR(KBr) vmax(cm^{-1}): 1666, 1574

^{1}H-NMR(d_6-DMSO) δ (ppm) : 8.57(1H, s), 8.50(1H, dd, J=8, 2Hz), 8.35(1H, dd, J=4, 2Hz), 8.23-8.56(8H, m), 6.88(2H, d, J=9Hz), 5.63(2H, s), 3.70 (3H, s)

MS m/e: 382(M^+), 381, 121

Example 46

3-(3-Methoxyphenyl)methyl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 46)

Melting point (solvent for recrystallization): 209 -210°C (DMF-water)

Elemental analysis (%): $C_{23}H_{18}N_4O_2$			
Calcd.:	C 72.24,	H 4.74,	N 14.65
Found :	C 72.40,	H 4.52,	N 14.61

IR(KBr) vmax(cm^{-1}): 1667, 1574

^{1}H-NMR(d_6-DMSO) δ (ppm) : 8.59(1H, s), 8.52(1H, dd, J=8, 2Hz) , 8.35(1H, dd, J=4, 2Hz) , 7.18-7.57 (7H, m) , 6.82-6.98(3H, m) , 5.68(2H, s) , 3.71(3H, s)

MS m/e: 382(M^+), 381

Example 47

3-(3-Nitrophenyl)methyl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 47)

Melting point (solvent for recrystallization): 284 - 289°C (DMF-water)

Elemental analysis (%): $C_{22}H_{15}N_5O_3$			
Calcd.:	C 66.49,	H 3.80,	N 17.62
Found :	C 66.42,	H 3.45,	N 17.67

IR(KBr) vmax(cm^{-1}) : 1662, 1527

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.68(1H, s), 8.52(1H, dd, j=8, 2Hz), 8.36(1H, dd, J=4, 2Hz), 8.25(1H, d, J= 2Hz) , 8.11-8,16(1H, m) , 7.73-7.82(1H, m) , 7.23-7.67(7H, m), 5.84(2H, s)

MS m/e: 397(M^+) , 396

Example 48

3-(2-Chlorophenyl)methyl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 48)

Melting point (solvent for recrystallization): 257 -262°C (DMF-water)

Elemental analysis (%): $C_{22}H_{15}N_4OCl$			
Calcd.:	C 68.39,	H 3.91,	N 14.50
Found :	C 68.51,	H 3.91,	N 14.80

IR(KBr) vmax(cm^{-1}): 1664, 1557

^{1}H-NMR(d_6-DMSO) δ(ppm): 8.56(1H, dd, J=8, 2Hz), 8.50 (1H, s), 8.38(1H, dd, J=4, 2Hz), 7.15-7.57(9H, m) , 6.86(1H, d, J=7Hz) , 5. 83(2H, s)

MS m/e: 388, 387, 386(M^+), 385, 352, 351

Example 49

3-(3-Bromophenyl)methyl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 49)

Melting point (solvent for recrystallization): 244 -246°C (DMF-water)

Elemental analysis (%): $C_{22}H_{15}N_4OBr$			
Calcd.:	C 61.27,	H 3.51,	N 12.99
Found :	C 61.20,	H 3.40,	N 12.81

IR(KBr) vmax(cm^{-1}): 1666, 1575

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.64(1H, s), 8.53(1H, dd, J= 8, 2Hz), 8.37(1H, dd, J=4, 2Hz), 7.23-7.60(10H, m), 5.71(2H, s)

MS m/e: 432, 431, 430, 429(M^+)

Example 50

3-(4-Methoxycarbonylphenyl)methyl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 50)

Elemental analysis (%): $C_{24}H_{18}N_4O_3$			
Calcd.:	C 70.23,	H 4.42,	N 13.65
Found :	C 70.65,	H 4.43,	N 13.55

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.63(1H, s), 8.54(1H, dd, J=8, 2Hz), 8.37(1H, dd, J=4, 2Hz), 7.93(2H, d, J=12Hz), 7.22-7.55(8H, m), 5.81(2H, s), 3.83 (3H, s)

MS m/e: 410(M^+), 409

Example 51

3-(3-Hydroxypropyl)-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 51)

Melting point (solvent for recrystallization): 248 -252°C (chloroform-isopropyl ether)

Elemental analysis (%): $C_{18}H_{16}N_4O_2 \cdot 0.3H_2O$			
Calcd.:	C 66.37,	H 5.14,	N 17.20
Found :	C 66.50,	H 4.98,	N 17.22

IR(KBr) vmax(cm^{-1}): 3676, 3650, 1587

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.52(1H, dd, J=8, 2Hz), 0.39 (1H, s), 8.35(1H, dd, J=4, 2Hz), 7.23-7.58(6H, m), 4.51(2H, t, J=7Hz), 3.41(2H, t, J=7Hz), 1.92-2.04(2H, m)

MS m/e: 320(M^+), 319, 275

Example 52

3-(2-Hydroxypropyl)-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 52)

Melting point (solvent for recrystallization): 95 -98°C (chloroform-isopropyl ether)

Elemental analysis (%): $C_{18}H_{16}N_4O_2 \cdot 0.4H_2O$			
Calcd.:	C 66.00,	H 5.17,	N 17.10
Found :	C 66.04,	H 5.00,	N 16.64

IR(KBr) vmax(cm^{-1}): 3676, 3630, 1662

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.53(1H, dd, J=8, 2Hz), 8.30-8.37(2H, m), 7.27-7.57(6H, m), 4.40-4.60 (2H, m), 3.78-3.92(1H, m), 3.45-3.70(1H, m), 1.10(3H, d, J=6Hz)

MS m/e: 320, 319, 303, 261

Example 53

3-Furfuryl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 53)

Melting point (solvent for recrystallization): 252 -253°C (chloroform-isopropyl ether)

Elemental analysis (%): $C_{20}H_{14}N_4O_2$			
Calcd.:	C 70.17,	H 4.12,	N 16.37
Found :	C 70.10,	H 3.98,	N 16.25

^{1}H-NMR(d_6-DMSO) δ (ppm) : 8.52(1H, dd, J=8, 2Hz), 8.46 (1H, s), 8.36(1H, dd, J=4, 2Hz), 7.61-7.63(1H, m), 7.42-7.56(3H, m), 7.27-7.38(3H, m), 6.41-6.47 (2H, m), 5.76(2H, s)

MS m/e: 342(M^+), 341, 81

Example 54

5-Phenyl-3-(3-pyridyl)methyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 54)

Melting point (solvent for recrystallization): 273 -277°C (chloroform-isopropyl ether)

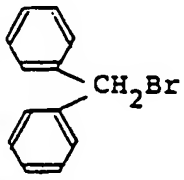
Elemental analysis (%): $C_{21}H_{15}N_5O$			
Calcd.:	C 71.38,	H 4.28,	N 19.82
Found :	C 71.43,	H 4.19,	N 19.74

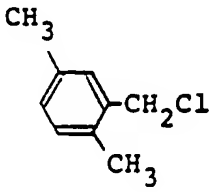
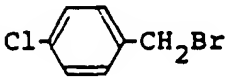
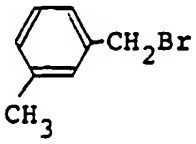
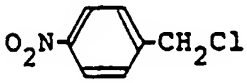
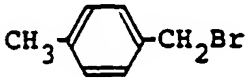
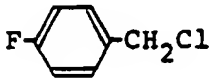
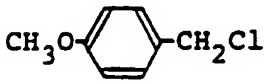
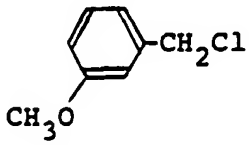
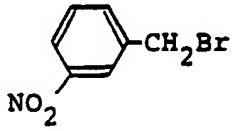
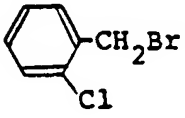
IR(KBr) vmax(cm^{-1}): 2740, 1662

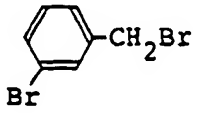
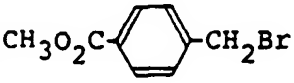
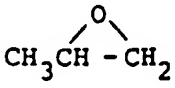
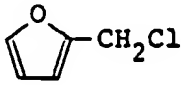
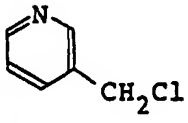
^{1}H-NMR(d_6-DMSO) δ (ppm): 8.64(2H, s), 8.45-8.53(2H, m) 8.36(1H, dd, J=4, 2Hz), 7.76 (1H, d, J=8Hz), 7.26-7.60(8H, m), 5.76(2H, s)

MS m/e: 353(M^+), 352

Table 9

Compound	Compound used instead of methyl iodide	Yield (%)
30	$CH_3CH_2CH_2CH_2CH_2CH_2I$	83
31	$CH_3CH_2OCH_2CH_2Br$	95
32	$CH_3CH_2O\overset{\overset{O}{\|}}{C}CH_2Cl$	77
33	$CH_2=CHCH_2Br$	74
34	$CH_3\overset{\overset{O}{\|}}{C}OCH_2CH_2Br$	57
35	$(CH_3CH_2CH_2)_2CHOSO_2$-C$_6$H$_4$-CH_3	62
36	C$_6$H$_5$-$CH=CHCH_2Br$	81
37	C$_6$H$_5$-CH_2Br	74
38		54

Compound	Compound used instead of methyl iodide	Yield (%)
39		72
40		93
41		87
42		98
43		94
44		65
45		56
46		76
47		78
48		75

Compound	Compound used instead of methyl iodide	Yield (%)
49		80
50		51
51	$HOCH_2CH_2CH_2Br$	30
52		63
53		59
54		68

In Examples 55 -61, the same procedure as in Example 13 was repeated except that the compounds shown in Table 10 were used respectively instead of Compound 3.

Example 55

5-(4-Methoxyphenyl)-3-benzyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 55)

Melting point (solvent for recrystallization): 299°C (chloroform-isopropyl ether)

Elemental analysis (%): $C_{23}H_{18}N_4O_2$			
Calcd.:	C 72.24,	H 4.74,	N 14.65
Found :	C 72.51,	H 4.80,	N 14.41

IR(KBr) vmax(cm^{-1}): 1667

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.59(1H, s), 8.52(1H, dd, J=8, 2Hz), 8.37(1H, dd, J=4, 2Hz), 7.22-7.38(6H, m), 7.19 (2H, dd, J=7, 2Hz), 7.05(2H, dd, J=7, 2Hz), 5.71(2H, s), 3.83(3H, s)

MS m/e: 382(M^+), 381

Example 56

5-(3-Methoxenyl)-3-benzyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 56)

Melting point (solvent for recrystallization): 281 -282°C (chloroform-isopropyl ether)

Elemental analysis (%): $C_{23}H_{18}N_4O_2$			
Calcd.:	C 72.24,	H 4.74,	N 14.65
Found :	C 71.90,	H 4.61,	N 14.48

IR(KBr) vmax(cm^{-1}): 1667, 1515

^{1}H-NMR(d_6-DMSO) δ (ppm) : 8.59(1H, s), 8.52(1H, dd, J=8, 2Hz), 8.38(1H, dd, J=4, 2Hz), 7.25-7.46(7H, m), 7.04(H, dd, J=8, 2Hz), 6.84-6.91(2H, m), 5.72 (2H, s), 3.77(3H, s)

MS m/e: 382(M^+), 381

Example 57

5-(4-Methylphenyl)-3-benzyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 57)

Melting point (solvent for recrystallization): 253°C (chloroform-isopropyl ether)

Elemental analysis (%): $C_{23}H_{18}N_4O$			
Calcd.:	C 75.39,	H 4.95,	N 15.29
Found :	C 75.40,	H 4.84,	N 15.33

IR(KBr) vmax(cm^{-1}) : 1664, 1574

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.59(1H, s), 8.52(1H, dd, J=8, 2Hz), 8.35(1H, dd, J=4, 2Hz), 7.25-7.38(8H, m), 7.15(2H, d, J=8Hz), 5.72(2H, s), 2.41 (3H, s)

MS m/e: 366(M^+), 365

Example 58

5-(3-Methylphenyl)-3-benzyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 58)

Melting point (solvent for recrystallization): 190 -192°C (chloroform-isopropyl ether)

Elemental analysis (%): $C_{23}H_{18}N_4O$			
Calcd.:	C 75.39,	H 4.95,	N 15.29
Found :	C 75.38,	H 5.06,	N 15.17

IR(KBr) vmax(cm^{-1}): 1667, 936

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.60(1H, s), 8.52(1H, dd, J=8, 2Hz), 8.37(1H, dd, J=4, 2Hz), 7.24-7.44(7H, m), 7.04-7.09(2H, m), 5.71(2H, s), 2.36(3H, s)

MS m/e: 366(M^+), 365

Example 59

5-(3-Chlorophenyl)-3-benzyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 59)

Melting point (solvent for recrystallization): 228°C (chloroform-isopropyl ether)

Elemental analysis (%): $C_{22}H_{15}N_4OCl$			
Calcd.:	C 68.31,	H 3.91,	N 14.48
Found :	C 68.19,	H 3.69,	N 14.46

IR(KBr) vmax(cm^{-1}): 1668

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.61(1H, s), 8.53(1H, dd, J=8, 2Hz), 8.38(1H, dd, J=4, 2Hz), 7.48-7.57(3H, m), 7.25-7.40(7H, m), 5.72(2H, s)

MS m/e: 388, 387, 386(M^+), 385

Example 60

2-Methyl-5-phenyl-3-benzyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 60)

Melting point (solvent for recrystallization): 267 -269°C (ethanol-water)

Elemental analysis (%): $C_{23}H_{18}N_4O$			
Calcd.:	C 75.39,	H 4.95,	N 15.29
Found :	C 75.28,	H 4.91,	N 14.84

IR(KBr) vmax(cm^{-1}): 3648, 3362, 1615, 1594

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.51(1H, dd, J=8, 2Hz), 8.39 (1H, dd, J=4, 2Hz), 7.19-7.56 (11H, m), 5.79(2H, s), 2.52(3H, s)

MS m/e: 368, 367, 366, 365(M^+)

Example 61

2,5-Diphenyl-3-benzyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 61)

Melting point (solvent for recrystallization): 283 -287°C (DMF-water)

Elemental analysis (%): $C_{28}H_{20}N_4O$			
Calcd.:	C 78.49,	H 4.70,	N 13.08
Found :	C 78.68,	H 4.71,	N 12.72

IR(KBr) vmax(cm^{-1}): 1664

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.62(1H, dd, J=8, 2Hz), 8.41 (1H, dd, J=4, 2Hz), 7.71(2H, dd, J=7, 2Hz), 7.18-7.61(12H, m), 6.97(2H, dd, J=7, 2Hz), 5.88(2H, s)

MS m/e: 429, 428(M^+), 427, 91

Table 10

Compound	Starting Compound	Yield (%)
55	Compound 22	75
56	Compound 23	84
57	Compound 24	67
58	Compound 25	40
59	Compound 26	65
60	Compound 18	70
61	Compound 19	93

In Examples 62 -65, the same procedure as in Example 12 was repeated except that the compounds shown in Table II were used respectively instead of Compound 3.

Example 62

3-Isobutyl-5-(4-methoxyphenyl)-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 62)

Melting point (solvent for recrystallization): 232 -235°C (chloroform-isopropyl ether)

Elemental analysis (%): $C_{20}H_{20}N_4O_2$			
Calcd.:	C 68.75,	H 5.79,	N 16.08
Found :	C 68.67,	H 5.86,	N 15.86

IR(KBr) vmax(cm^{-1}): 1676, 1575

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.51(1H, dd, J=8, 2Hz), 8.39 (1H, s), 8.36(1H, dd, J=4, 2Hz), 7.35(1H, dd, J= 8, 4Hz), 7.20(2H, d, J=9Hz), 7.06(2H, d, J=9Hz), 4.26(2H, d, J=7Hz), 3.85(3H, s), 2.09-2.24(1H, m), 0.87(6H, d, J=7Hz)

MS m/e: 348(M^+), 347, 292, 291

Example 63

3-Isobutyl-5-(3-methoxyphenyl)-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 63)

Melting point (solvent for recrystallization): 233 -234°C (chloroform-isopropyl ether)

Elemental analysis (%): $C_{20}H_{20}N_4O_2$			
Calcd.:	C 68.94,	H 5.78,	N 16.08
Found :	C 68.92,	H 5.84,	N 16.07

IR(KBr) vmax(cm^{-1}) : 1668, 1511

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.52(1H, dd, J=8, 2Hz), 8.41 (1H, s), 8.38(1H, dd, J=4, 2Hz), 7.34-7.47(2H, m), 7.04(1H, dd, J=8, 2Hz), 6.85-6.92 (2H, m), 4.26 (2H, d, J=7Hz), 3.78(3H, s), 2.08-2.25(1H, m), 0.87(6H, d, J=7Hz)

MS m/e: 348(M^+), 347, 292, 291

Example 64

3-Isobutyl-5-(4-methylphenyl)-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 64)

Melting point (solvent for recrystallization): 193 -195°C (chloroform - isopropyl ether)

Elemental analysis (%): $C_{20}H_{20}N_4O \cdot 0.2H_2O$			
Calcd.:	C 71.49,	H 6.12,	N 16.67
Found :	C 71.39,	H 6.01,	N 16.42

IR(KBr) vmax(cm^{-1}): 1664, 1602, 1574

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.52(1H, dd, J=8, 2Hz), 8.40(1H, s), 8.36(1H, dd, J=4, 2Hz), 7.31-7.37 (3H, m), 7.16(2H, d, J=8Hz), 4.26(2H, d, J=7Hz), 2.42(3H, s), 2.08-2.24(1H, m), 0.86(6H, d, J=7Hz)

MS m/e: 332(M^+), 331, 276, 275

Example 65

3-Isobutyl-5-(3-methylphenyl)-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 65)

Melting point (solvent for recrystallization): 177 - 178°C (chloroform-isopropyl ether)

Elemental analysis (%): $C_{20}H_{20}N_4O \cdot 0.3H_2O$			
Calcd.:	C 71.11,	H 6.15,	N 16.59
Found :	C 71.24,	H 6.12,	N 16.53

IR(KBr) vmax(cm^{-1}) : 1662

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.52(1H, dd, J=8, 2Hz), 8.40 (1H, s), 8.37(1H, dd, J=4, 2Hz), 7.32-7.44(2H, m), 7.27(1H, d, J=7Hz), 7.05-7.10(2H, m), 4.26(2H, d, J=7Hz), 2.38(3H, s), 2.08-2.24(1H, m), 0.87 (6H, d, J=7Hz)

MS m/e: 332(M^+), 331, 276, 275

Table 11

Compound	Starting Compound	Yield (%)
62	Compound 22	20
63	Compound 23	6
64	Compound 24	49
65	Compound 25	4

Example 66

3-(3-Morpholino)propyl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one hydrochloride (Compound 66)

Morpholine (30 ml) was added to 2.0 g (4.7 mmol) of Compound 69 obtained in Example 69, and the mixture was stirred at room temperature for one hour. After addition of water, extraction was carried out with chloroform. The organic layer was removed by extraction with 2N hydrochloric acid. The water layer was adjusted to pH 11 with 8N sodium hydroxide, followed by extraction with chloroform. The organic layer was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure. To the obtained crude product was added ethyl acetate saturated with hydrogen chloride, and the formed crystals were taken by filtration and dried to give 1.0 g (yield 55%) of Compound 66.

Melting point: 294 -297°C

Elemental analysis (%): $C_{22}H_{23}N_5O_2 \cdot 2.0HCl \cdot 1.4H_2O$			
Calcd.:	C 54.19,	H 5.75,	N 14.36
Found :	C 54.12,	H 5.79,	N 14.43

IR(KBr) vmax(cm^{-1}): 3676, 2346, 1695

^{1}H-NMR(d_6-DMSO) δ (ppm) : 11.51(1H, br.s), 8.87(1H, s), 8.67(1H, dd, J=8, 2Hz), 8.40(1H, dd, J=4, 2Hz), 7.28-7.63 (6H, m), 4.45-4.80(2H, m), 3.77-4.02 (4H, m), 3.32-3.49(2H, m), 2.92-3.22(4H, m), 2.30-2.48(2H, m)

MS m/e: 390, 389(M^+), 388, 276, 275, 100

Example 67

3-(3-Diethylamino)propyl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one hydrochloride (Compound 67)

Compound 67 was obtained according to the same procedure as in Example 66 except that diethylamine was used instead of morpholine (yield 69%).

Melting point: 152 - 153°C

Elemental analysis (%): $C_{22}H_{25}N_5O \cdot 2.0HCl \cdot 1.3H_2O$			
Calcd.:	C 56.01,	H 6.32,	N 14.84
Found :	C 55.95,	H 6.19,	N 14.70

IR(KBr) vmax(cm^{-1}): 3734, 3688, 3676, 3648, 771

^{1}H-NMR(d_6-DMSO) δ (ppm): 10.57(2H, br.s), 8.68(1H, s), 8.60(1H, dd, J=8, 2Hz), 8.39(1H, dd, J=4, 2Hz), 7.22-7.60 (6H, m), 4.60(2H, t, J=7Hz), 2.91-3.14 (6H, m), 2.20-2.35(2H, m), 1.18(6H, t)

MS m/e: 376, 375(M^+), 347, 346, 314, 303, 86

Example 68

3-(3-Chloropropyl)-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 68)

Compound 68 was obtained according to the same procedure as in Example 4 except that 1-bromo-3-chloropropane was used instead of methyl iodide (yield 92%).

Melting point (solvent for recrystallization): 186 -190°C (ethyl acetate-n-hexane)

Elemental analysis (%): $C_{18}H_{15}N_4OCl \cdot 0.2H_2O$			
Calcd.:	C 63.14,	H 4.53,	N 16.36
Found :	C 63.09,	H 4.30,	N 16.34

IR(KBr) vmax(cm^{-1}): 2958, 1650, 1575

^{1}H-NMR($CDCl_3$) δ (ppm): 8.62(1H, dd, J=8, 2Hz), 8.41 (1H, dd, J=4, 2Hz), 8.01(1H, s), 7.11-7.62(6H, m), 4.67(2H, t, J=7Hz), 3.53(2H, t, J=7Hz), 2.30-2.55 (2H, m)

MS m/e: 340, 339, 338(M^+), 337

Example 69

3-(3-Iodopropyl)-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (Compound 69)

To 200 ml of acetonitrile were added 18 g (0.052 mol) of Compound 68 obtained in Example 68 and 12 g (0.078 mol) of sodium iodide, and the mixture was refluxed for 24 hours. In the course of refluxing, 7.8 g (0.052 mol) of sodium iodide was added to the mixture. After cooling, the solvent was evaporated under reduced pressure and water was added to the residue. Then, extraction was carried out with chloroform, and the organic layer was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure to obtain a crude product. Recrystallization from ethyl acetate-n-hexane gave 16 g (yield 73%) of Compound 69.

^{1}H-NMR($CDCl_3$) δ (ppm): 8.59(1H, dd, J=8, 2Hz), 8.42 (1H, dd, J=4, 2Hz), 8.03(1H, s), 7.28-7.72(6H, m), 4.60(2H, t, J=7Hz), 3.12(2H, t, J=7Hz), 2.30-2.61 (2H, m)

Example 70 Tablets

Tablets each having the following composition, are prepared in a conventional manner.

Compound 1	100 mg
Lactose	60 mg
Potato starch	30 mg
Polyvinyl alcohol	2 mg
Magnesium stearate	1 mg
Tar pigment	trace

Example 71 Powder

Powder having the following composition is prepared in a conventional manner.

Compound 2	100 mg
Lactose	30 mg

Example 72 Syrup

Syrup having the following composition is prepared in a conventional manner.

Compound 1	100 mg
Refined sugar	30 g
Ethyl p-hydroxybenzoate	40 mg
Propyl p-hydroxybenzoate	10 mg
Strawberry flavor	0.1 ml

Water is added to the composition to make the whole volume 100 cc.

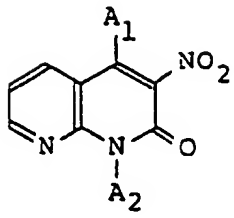
Example 73 Syrup

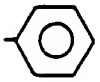
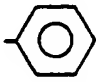
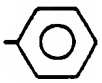
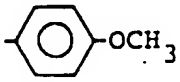
Syrup having the following composition is prepared in a conventional manner.

Compound 2	100 mg
Refined sugar	30 g
Ethyl p-hydroxybenzoate	40 mg
Propyl p-hydroxybenzoate	10 mg
Strawberry flavor	0.1 ml

Water is added to the composition to make the whole volume 100 ml.
The compounds obtained in Reference Examples are shown in Table 12.

Table 12-1



Reference Example No.	Compound No.	A_1	A_2
1	a	-Cl	
2	b	$-NHCH_3$	"
3	c	$-NH_2$	"
4	d	-Cl	$-(CH_2)_3CH_3$
5	e	$-NHCH_3$	"
6	h	$-NHC_2H_5$	
7	i	$-NH(CH_2)_2CH_3$	"
8	j		"
9	k	$-NH_2$	$-(CH_2)_3CH_3$
15	m - 1	-OH	

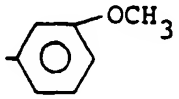
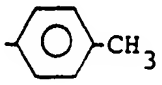
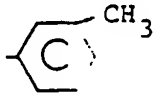
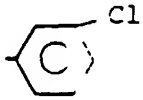
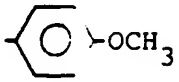
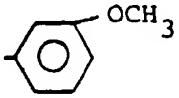
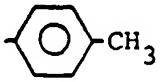
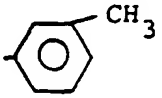
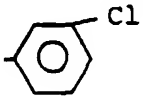
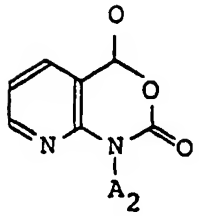
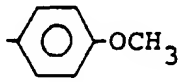
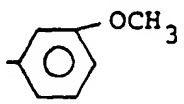
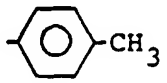
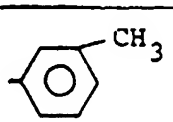
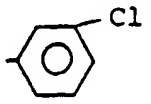
Reference Example No.	Compound No.	A_1	A_2
16	m - 2	-OH	
17	m - 3	"	
18	m - 4	"	
19	m - 5	"	
20	n - 1	$-NH_2$	
21	n - 2	"	
22	n - 3	"	
23	n - 4	"	
24	n - 5	"	

Table 12-2



Reference Example No.	Compound No.	A_2
10	ℓ - 1	
11	ℓ - 2	
12	ℓ - 3	
13	ℓ - 4	
14	ℓ - 5	

Reference Example 1

4-Chloro-3-nitro-1-phenyl-1,8-naphthyridin-2(H)-one (Compound a)

(A) 1-Phenyl-2H-pyrido[2,3-d][1,3]oxazine-2,4(1H)-dione (Compound p)

In a mixture of 70 ml of 1,2-dichloroethane and 7 ml of dioxane was dissolved 7.0 g (0.031 mol) of methyl 2-anilinonicotinate [J. Org. Chem., 39, 1803 (1974)]. After 11 ml (0.092 mol) of trichloromethyl chloroformate was added dropwise to the solution at 60°C with stirring, the mixture was refluxed for 3 hours. The mixture was slightly cooled and 0.25 g of activated carbon was added thereto, followed by refluxing for further 30 minutes in a nitrogen flow. The mixture was cooled to room temperature, filtered and concentrated to form crystals. Recrystallization from methylene chloride-isopropyl ether gave 6.5 g (yield 87%) of 1-phenyl-2H-pyrido[2,3-d][1,3]oxazine-2,4(1H)-dione (Compound p) as colorless crystals.

Melting point: 196 -198°C

Elemental analysis (%): $C_{13}H_8N_2O_3$			
Calcd.:	C 65.00,	H 3.36,	N 11.66
Found :	C 65.11,	H 3.22,	N 11.48

IR(KBr) νmax(cm^{-1}): 1791, 1727, 1584
^{1}H-NMR($CDCl_3$) δ (ppm): 8.58(1H, dd, J=5, 2Hz), 8.48 (1H, dd, J=8, 2Hz), 7.51-7.63(3H, m), 7.33-7.38 (2H, m), 7.29(1H, dd, J=8, 5Hz)
MS m/e : 240(M^+), 196, 168

(B) 4-Hydroxy-3-nitro-1-phenyl-1,8-naphthyridin-2(1H)-one (Compound f)

In 25 ml of N,N-dimethylacetamide was dissolved 1.9 ml (0.020 mol) of ethyl nitroacetate, and 0.80 g (0.020 mol) of 60% sodium hydride was added to the solution under ice cooling. After evolution of hydrogen ceased, 4.0 g (0.017 mol) of Compound p obtained was added and the mixture was slowly heated, followed by stirring at 100°C for 30 minutes. The solvent was distilled off under reduced pressure and 200 ml of water was added to the residue. After washing with ethyl acetate, the aqueous layer was made acidic with conc. hydrochloric acid. The precipitated crystals were taken by filtration. Recrystallization from isopropyl alcohol-ethanol gave 3.6 g (yield 77%) of 4-hydroxy-3-nitro-1-phenyl-1,8-naphthyridin-2 (Compound f) as light yellow needles.

Melting point: 296 -298°C

Elemental analysis (%): $C_{14}H_9N_3O_4$			
Calcd.:	C 59.37,	H 3.20,	N 14.84
Found :	C 59.57,	H 2.99,	N 14.68

IR(KBr) νmax(cm^{-1}): 1682, 1587, 1410
^{1}H-NMR(d_6-DMSO) δ (ppm): 8.50(1H, dd, J=8, 2Hz), 8.48 (1H, dd, J=4, 2Hz), 7.41-7.54(3H, m), 7.26-7.36 (3H, m)
MS m/e : 283(M^+), 282, 265, 77

(C) 4-Chloro-3-nitro-1-phenyl-1,8-naphthyridin-2(1H)-one (Compound a)

Compound f obtained (10 g, 0.038 mol) was suspended in 50 ml (0.54 mol) of phosphorus oxychloride, and the suspension was heated at 100°C for one hour. After the solvent was distilled off under reduced pressure, 4N sodium hydroxide solution was added under ice cooling for neutralization. The precipitated crystals were taken by filtration to give 5.2 g (yield 49%) of Compound a as white crystals.

Melting point (solvent for recrystallization): 228 -232°C (ethyl acetate-n-hexane)

Elemental analysis (%): $C_{14}H_8ClN_3O_3$			
Calcd.:	C 55.74,	H 2.21,	N 13.63
Found :	C 55.91,	H 2.68,	N 13.97

IR(KBr) νmax(cm^{-1}): 1667, 1587, 1547
^{1}H-NMR($CDCl_3$) δ (ppm): 8.62(1H, dd, J=4, 2Hz), 8.54 (1H, dd, J=8, 2Hz), 8.50-8.65 (3H, m), 7.41(1H, dd, J=8, 4Hz), 7.25-7.33(2H, m)
MS m/e : 300, 302(M^+)

Reference Example 2

4-Methylamino-3-nitro-1-phenyl-1,8-naphthyridin-2(1H)-one (Compound b)

In 60 ml of tetrahydrofuran was dissolved 1.8 g (6.0 mmol) of Compound a obtained in Reference Example 1, and 4.6 ml (60 mmol) of 40% aqueous solution of methylamine was added to the solution, followed by stirring at room temperature for 30 minutes. The solvent was distilled off under reduced pressure and 100 ml of water was added to

the residue. The precipitated crystals were taken by filtration and dried to give 1.6 g (yield 97%) of Compound b as light yellow crystals.

Melting point (solvent for recrystallization): >300°C (DMF-water)

Elemental analysis (%): $C_{15}H_{12}N_4O_3$			
Calcd.:	C 60.93,	H 3.94,	N 19.07
Found :	C 60.81,	H 4.08,	N 18.71

IR(KBr) νmax(cm^{-1}): 1620, 1588

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.64(1H, dd, J=8, 2Hz), 8.45 (1H, dd, J=4, 2Hz), 8.05-8.16 (1H, m), 7.42-7.55 (3H, m), 7.37(1H, dd, J=8, 4Hz), 7.22-7.29(2H, m), 2.88(3H, d, J=5Hz)

MS m/e : 296(M^+), 261

Reference Example 3

4-Amino-3-nitro-1-phenyl-1,8-naphthyridin-2(1H)-one (Compound c)

Compound c was obtained as light yellow crystals according to the same procedure as in Reference Example 2 except that aqueous ammonia was used instead of methylamine (yield 86%).

Melting point: >300°C

Reference Example 4

1-(n-Butyl)-4-chloro-3-nitro-1,8-naphthyridin-2(1H)-one (Compound d)

Phosphorus oxychloride (20 ml, 0.21 mol) was added to 2.0 g (7.6 mmol) of 1-n-butyl-4-hydroxy-3-nitro-1,8-naphthyridin-2(1H)-one [J. Heterocyclic Chem., 22, 193 (1985)], and the mixture was heated to reflux for 30 minutes. After cooling to room temperature, the solvent was distilled off under reduced pressure and ice water was added to the resulting residue. The mixture was neutralized with 4N aqueous solution of sodium hydroxide, followed by extraction with chloroform. The organic layer was dried over anhydrous sodium sulfate, and then filtered. The solvent was distilled off under reduced pressure. The obtained residue was purified by silica gel column chromatography (developing solvent: chloroform/methanol = 20/1) to give 1.2 g (yield 56%) of Compound d as colorless crystals.

Elemental analysis (%): $C_{12}H_{12}ClN_3O_3$			
Calcd.:	C 51.30,	H 4.02,	N 14.93
Found :	C 51.16,	H 4.29,	N 14.92

^{1}H-NMR($CDCl_3$) δ (ppm): 8. 78 (1H, dd, J=4, 2Hz), 8.38 (1H, dd, J=8, 2Hz), 7.39(1H, dd, J=8, 4Hz), 4.56 (2H, t, J=7Hz), 1.25-1.76(4H, m), 0.97(2H, t, J=7Hz)

MS m/e : 266, 264(M^+-OH), 208, 206

Reference Example 5

1-(n-Butyl)-4-methylamino-3-nitro-1,8-naphthyridin-2(1H)-one (Compound e)

Compound e was obtained as light yellow crystals in an amount of 2.7 g (yield 90%) according to the same procedure as in Reference Example 2 except that 3 g (11 mmol) of Compound d obtained in Reference Example 4 was used instead of Compound a.

Elemental analysis (%): $C_{13}H_{16}N_4O_3$			
Calcd.:	C 56.57,	H 5.87,	N 20.41
Found :	C 56.51,	H 5.84,	N 20.28

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.71(1H, dd, J=4, 2Hz), 8.58 (1H, dd, J=8, 2Hz), 7.75-8.02(1H, m), 7.38(1H, dd, J=8, 4Hz), 4.31(2H, t, J=7Hz), 1.12-1.79(4H, m), 0.91(3H, t, J=7Hz)

MS (m/e): 259(M^+-OH), 241, 187

Reference Example 6

4-Ethylamino-3-nitro-1-phenyl-1,8-naphthyridin-2(1H)-one (Compound h)

Compound h was obtained according to the same procedure as in Reference Example 2 except that ethylamine was used instead of methylamine.

Melting point (solvent for recrystallization): 189 -193°C (DMF-water)

Elemental analysis (%): $C_{16}H_{14}N_4O_3$			
Calcd.:	C 61.79,	H 4.53,	N 17.78
Found :	C 61.93,	H 4.55,	N 18.06

IR(KBr) vmax(cm^{-1}): 1617

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.72(1H, dd, J=8, 2Hz), 8.42 (1H, dd, J=4, 2Hz), 7.06-7.71 (6H, m), 3.11-3.29 (2H, m), 1.26(3H, t, J=7Hz)

MS (m/e) : 310(M^+), 297, 275

Reference Example 7

4-Isopropylamino-3-nitro-1-phenyl-1,8-naphthyridin-2(1H)-one (Compound i)

Compound i was obtained according to the same procedure as in Reference Example 2 except that isopropylamine was used instead of methylamine.

Melting point (solvent for recrystallization): 257 -261°C (ethanol-water)

Elemental analysis (%): $C_{17}H_{16}N_4O_3$			
Calcd.:	C 63.19,	H 4.86,	N 17.04
Found :	C 62.97,	H 4.97,	N 17.27

IR(KBr) vmax(cm^{-1}): 1659, 1607

^{1}H-NMR(d_6-DMSO) δ (ppm) : 8.51(1H, dd, J=4, 2Hz), 8.20 (1H, dd, J=8, 2Hz), 7.42-7.58 (3H, m), 7.23-7.29 (2H, m), 7.21(1H, dd, J=8, 4Hz), 6.93-7.05(1H, m), 4.02-4.20(1H, m), 1.40(6H, d, J=6Hz)

MS(m/e): 324(M^+), 306, 289, 222

Reference Example 8

4-Benzylamino-3-nitro-1-phenyl-1,8-naphthyridin-2(1H)-one (Compound j)

Compound j was obtained according to the same procedure as in Reference Example 2 except that benzylamine was used instead of methylamine.

Melting point (solvent for recrystallization): 192 -194°C (methanol-water)

Elemental analysis (%): $C_{21}H_{16}N_4O_3$			
Calcd.:	C 68.13,	H 4.24,	N 14.91
Found :	C 67.73,	H 4.33,	N 15.04

IR(KBr) vmax(cm^{-1}): 1616, 1519

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.80(1H, dd, J=8, 2Hz), 8.49 (1H, dd, J=4, 2Hz), 8.25-8.41 (1H, br.s), 7.18-7.56(11H, m), 4.44(2H, s)

MS(m/e) : 372(M^+) , 326, 91

Reference Example 9

4-Amino-1-n-butyl-3-nitro-1,8-naphthyridin-2(1H)-one (Compound k)

Compound k was obtained according to the same procedure as in Reference Example 5 except that aqueous ammonia was used instead of methylamine.

Elemental analysis (%): $C_{12}H_{14}N_4O_3$			
Calcd.:	C 55.07,	H 5.40,	N 4.36
Found :	C 54.96,	H 5.38,	N 21.36

^{1}H-NMR(d_6-DMSO) δ (ppm): 8.55-8.78(2H, m), 8.23(1H, br.s), 7.31(1H, dd, J=8, 4Hz), 4.27(2H, t, J=7Hz), 1.15-1.70 (4H, m), 0.91(3H, t, J=7Hz)

MS(m/e): 245(M^+-OH)

In Reference Examples 10 -14, the same procedure as in Reference Example 1-A was repeated except that the compounds shown in Table 13 were used respectively instead of methyl 2-anilinonicotinate.

Reference Example 10

1-(4-Methoxy)phenyl-2H-pyrido[2,3-d][1,3]oxazine-2,4(1H)-dione (Compound ℓ-1)

Melting point: 230 -233°C

Reference Example 11

1-(3-Methoxy)phenyl-2H-pyrido[2,3-d][1,3]oxazine-2,4(1H)-dione (Compound ℓ-2)

Melting point: 233 -235°C

Reference Example 12

1-(4-Methyl)phenyl-2H-pyrido[2,3-d][1,3]oxazine-2,4(1H)-dione (Compound ℓ-3)

Melting point: 240 -245°C

Reference Example 13

1-(3-Methyl)phenyl-2H-pyrido[2,3-d][1,3]oxazine-2,4(1H)-dione (Compound ℓ-4)

Melting point: 151 -154°C

Reference Example 14

1-(3-Chloro)phenyl-2H-pyrido[2,3-d][1,3]oxazine-2,4(1H)-dione (Compound ℓ-5)

Melting point: 230 -233°C

Table 13

Reference Example No.	Compound	Yield (%)
10	Methyl 2-(4-Methoxy)anilinonicotinate	92

Table 13 (continued)

Reference Example No.	Compound	Yield (%)
11	Methyl 2-(3-Methoxy)anilinonicotinate	72
12	Methyl 2-(4-Methyl)anilinonicotinate	93
13	Methyl 2-(3-Methyl)anilinonicotinate	79
14	Methyl 2-(3-Chloro)anilinonicotinate	72

In Reference Examples 15 -19, the same procedure as in Reference Example 1-B was repeated except that the compounds shown in Table 14 were used respectively instead of Compound p.

Reference Example 15

4-Hydroxy-1-(4-methoxy)phenyl-3-nitro-1,8-naphthyridin-2(1H)-one (Compound m-1)

Melting point: 220 -222°C

Reference Example 16

4-Hydroxy-1-(3-methoxy)phenyl-3-nitro-1,8-naphthyridin-2(1H)-one (Compound m-2)

Melting point: 216 -217°C

Reference Example 17

4-Hydroxy-1-(4-methyl)phenyl-3-nitro-1,8-naphthyridin-2(1H)-one (Compound m-3)

Melting point: 225 -226°C

Reference Example 18

4-Hydroxy-1-(3-methyl)phenyl-3-nitro-1,8-naphthyridin-2(1H)-one (Compound m-4)

Melting point: 206°C

Reference Example 19

4-Hydroxy-1-(3-chloro)phenyl-3-nitro-1,8-naphthyridin-2(1H)-one (Compound m-5)

Melting point: 189 -191°C

Table 14

Reference Example No.	Starting Compound (Number of Reference Example wherein the above compound is obtained)	Yield (%)
15	ℓ - 1 (10)	50
16	ℓ - 2 (11)	66
17	ℓ - 3 (12)	78
18	ℓ - 4 (13)	69
19	ℓ - 5 (14)	74

In Reference Examples 20 -24, the same procedure as in Reference Example 1-C was repeated except that the compounds shown in Table 15 were used respectively instead of Compound f.

Reference Example 20

4-Amino-1-(4-methoxy)phenyl-3-nitro-1,8-naphthyridin-2(1H)-one (Compound n-1)

Melting point: >300°C

Reference Example 21

4-Amino-1-(3-methoxy)phenyl-3-nitro-1,8-naphthyridin-2(1H)-one (Compound n-2)

Melting point: >300°C

Reference Example 22

4-Amino-1-(4-methyl)phenyl-3-nitro-1,8-naphthyridin-2(1H)-one (Compound n-3)

Melting point: >300°C

Reference Example 23

4-Amino-1-(3-methyl)phenyl-3-nitro-1,8-naphthyridin-2(1H)-one (Compound n-4)

Melting point: >300°C

Reference Example 24

4-Amino-1-(3-chloro)phenyl-3-nitro-1,8-naphthyridin-2(1H)-one (Compound n-5)

Melting point: >300°C

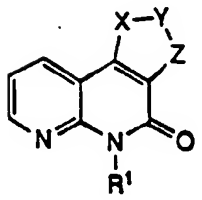
Table 15

Reference Example No.	Starting Compound (Number of Reference Example wherein the above compound is obtained)	Yield (%)
20	m - 1 (15)	78
21	m - 2 (16)	85
22	m - 3 (17)	84
23	m - 4 (18)	85
24	m - 5 (19)	70

Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

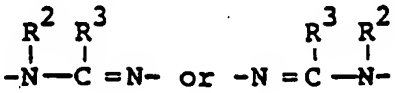
1. An imidazonaphthyridine derivative represented by formula (I) :



(I)

wherein:

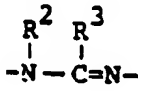
R^1 represents C_1-C_8 alkyl or substituted or unsubstituted phenyl or naphthyl; and
X-Y-Z represents



wherein R^2 represents hydrogen, C_1-C_8 alkyl, C_2-C_6 alkenyl, styryl or cinnamyl or -$C(R^5)H$-$(CH_2)_n$-R^4 (wherein R^4 represents substituted or unsubstituted phenyl or naphthyl, substituted or unsubstituted pyridyl, substituted or unsubstituted furyl, hydroxy-substituted C_1-C_8 alkyl, C_1-C_6 alkanoyloxy, morpholino, C_1-C_6 alkanoyl, carboxy, (C_1-C_8 alkoxy)carbonyl, C_3-C_8 cycloalkyl, hydroxy, C_1-C_8 alkoxy, halogen or NR^6R^7 wherein R^6 and R^7 independently represents hydrogen or C_1-C_8 alkyl; R^5 represents hydrogen, C_1-C_8 alkyl, or phenyl; and n represents an integer of 0 to 3); and R^3 represents hydrogen, mercapto, hydroxy, C_1-C_8 alkyl, or phenyl or naphthyl; whereby the substituents of phenyl, naphthyl, pyridyl and furyl may be one to three substituents selected from C_1-C_8 alkyl, C_1-C_8 alkoxy, nitro, (C_1-C_8 alkoxy)=carbonyl and halogen;

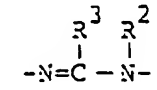
or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein X-Y-Z is



wherein R^2 is C_1-C_8 alkyl; and R^3 is hydrogen.

3. A compound according to claim 1, wherein X-Y-Z is



wherein R^2 is hydrogen, C_1-C_8 alkyl, C_2-C_6 alkenyl or -$C(R^5)H$-$(CH_2)_n$-R^4 (wherein R^4 represents substituted or unsubstituted phenyl or naphthyl, C_1-C_6 alkanoyloxy, (C_1-C_8 alkoxy)carbonyl, C_1-C_6 alkanoyl, substituted or unsubstituted pyridyl, or C_1-C_8 alkoxy; R^5 represents hydrogen; and n is 0 or 1); and R^3 represents hydrogen.

4. A compound according to claim 3, wherein R^1 is C_1-C_8 alkyl or phenyl; and R^2 is hydrogen, C_1-C_8 alkyl or -CH_2-R^4 (wherein R^4 is phenyl or naphthyl, pyridyl or C_1-C_6 alkanoyl).

5. A compound according to claim 1, namely

5-(n-butyl)-1-methyl-1H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one,
5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one, . 3-ethyl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one,
5-phenyl-3-n-propyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one,
3-benzyl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one,
3-acetyl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one,
5-n-butyl-3-n-propyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5)-one, or

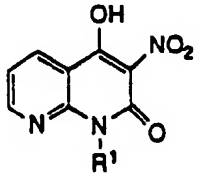
5-phenyl-3-(3-pyridyl)methyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5)-one.

6. A compound according to any of claims 1 to 4, wherein said salt is an acid addition salt, a metal salt, an ammonium salt, an organic amine addition salt or an amino acid addition salt.

7. A process for preparing an imidazonaphtyridine derivative represented by the formula (Ia)

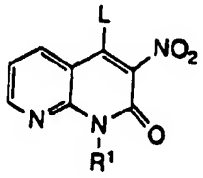
(Ia)

which comprises reacting a compound of the formula (II)



(II)

with sulfonyl chloride or a halogenating agent to yield a compound of the formula (III)

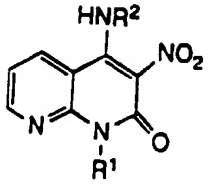


(III)

wherein L is sulfonyloxy or a halogen, which is further reacted with a compound of the formula (VII)

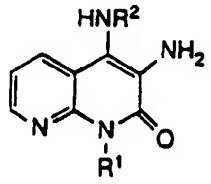
$$R^2NH_2 \qquad \text{(VII)}$$

to yield a compound of the formula (IV)



(IV)

which is reduced to a compound of the formula (V)

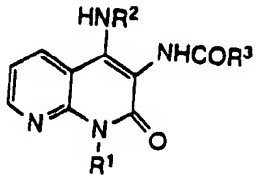


(V)

which is further reacted with a compound of the formula (IX)

$$R^3COOH \qquad (IX)$$

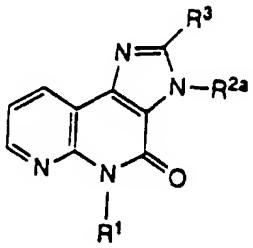
or a reactive derivative thereof to yield a compound of the formula (VI)



(VI)

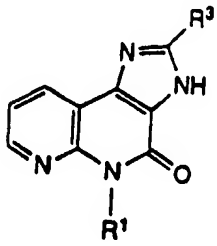
which is reacted in the presence of a cyclizing agent to the desired compound of the formula (Ia) which is optionally converted to a pharmaceutically acceptable salt thereof and wherein R^1, R^2 and R^3 in all of the above compounds are as defined in claim 1.

8. A process for preparing an imidazonaphtyridine derivative of the formula (Ib),



(Ib)

wherein R^{2a} is R^2 as defined in claim 1 with the exception of hydrogen, which comprises reacting a compound of the formula (I-1),



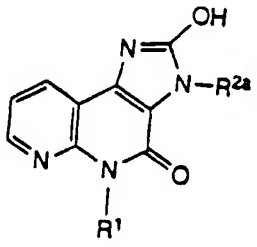
(I-1)

wherein R^1 and R^3 are as defined in claim 1, with a compound of the formula (X),

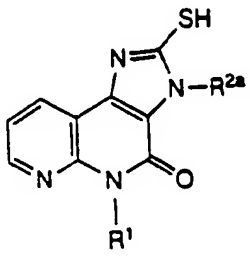
$$R^{2a}\text{-}L \qquad (X)$$

wherein R^{2a} is as defined above and L is as defined in claim 7 to yield the desired compound of the formula (Ib).

9. A process for preparing an imidazonaphtyridine derivative of the formula (Iba) which is represented by the formulae (Iba1) or (Iba2), respectively,



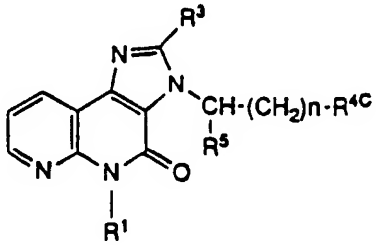
(Iba1)



(Iba2)

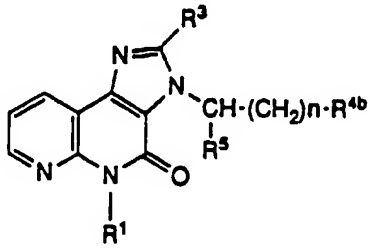
which comprises reacting a compound of the formula (V) as defined in claim 7 with carbonic acid dervative or a thiocarbonic acid derivative, respectively, to yield the desired compounds of the formula (Iba).

10. A process for preparing an imidazonaphtyridine derivative of the formula (Ic2),



(Ic2)

wherein R^1, R^3 and R^5 are as defined in claim 1 and R^{4c} is NR^6R^7, wherein R^6 and R^7 are as defined in claim 1, or morpholino, which comprises reacting a compound of the formula (Ic1)



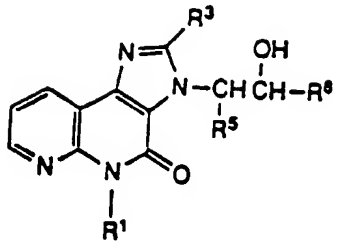
(Ic1)

wherein R^1, R^3 and R^5 are as defined above and R^{4b} is a halogen with a compound of the formula (XI),

$$R^{4c}\text{-}H \qquad \text{(XI)}$$

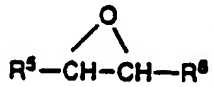
wherein R^{4c} is as defined above, to yield the desired compound of the formula (Ic2).

11. A process for preparing an imidazonaphtyridine derivative of the formula (Ic3),



(Ic3)

wherein R^1, R^3 and R^5 are as defined in claim 1 and R^8 is hydrogen or C_{1-7} alkyl, which comprises reacting a compound of the formula (I-1) as defined in claim 7 with a compound of the formula (XIII)



(XIII)

to yield the desired compound of the formula (Ic3).

12. Use of a compound of the formula (I) as defined in any of claims 1 to 6 for the preparation of a pharmaceutical composition.

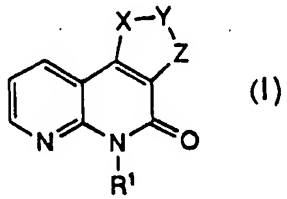
13. Use according to claim 12 wherein the composition has an anti-inflammatory, anti-allergic and/or broncho-dilative activity.

14. A pharmaceutical composition containing a compound of the formula (I) as defined in any of claims 1 to 6, their pharmaceutically acceptable salts or physiologically functional derivatives convertible in the body thereto and optionally a pharmaceutically acceptable carrier and/or diluent.

15. The composition of claim 14 showing an anti-inflammatory, anti-allergic and/or broncho-dilative activity.

Claims for the following Contracting State : ES

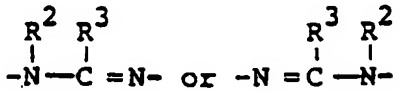
1. A process for preparing an imidazonaphthyridine derivative represented by formula (I):



(I)

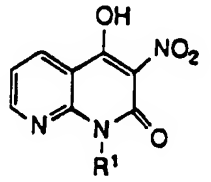
wherein:

R^1 represents C_1-C_8 alkyl or substituted or unsubstituted phenyl or naphthyl; and
X-Y-Z represents



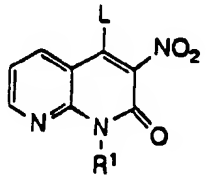
wherein R^2 represents hydrogen, C_1-C_8 alkyl, C_2-C_6 alkenyl, styryl or cinnamyl or -$C(R^5)H$-$(CH_2)_n$-R^4 (wherein R^4 represents substituted or unsubstituted phenyl or naphthyl, substituted or unsubstituted pyridyl, substituted or unsubstituted furyl, hydroxy-substituted C_1-C_8 alkyl, C_1-C_6 alkanoyloxy, morpholino, C_1-C_6 alkanoyl, carboxy, (C_1-C_8 alkoxy)carbonyl, C_3-C_8 cycloalkyl, hydroxy, C_1-C_8 alkoxy, halogen or NR^6R^7 wherein R^6 and R^7 independently represents hydrogen or C_1-C_8 alkyl; R^5 represents hydrogen, C_1-C_8 alkyl, or phenyl; and n represents an integer of 0 to 3); and R^3 represents hydrogen, mercapto, hydroxy, C_1-C_8 alkyl, or phenyl or naphthyl; whereby the substituents of phenyl, naphthyl, pyridyl and furyl may be one to three substituents selected from C_1-C_8 alkyl, C_1-C_8 alkoxy, nitro, (C_1-C_8 alkoxy)=carbonyl and halogen;

or a pharmaceutically acceptable salt thereof; which comprises reacting a compound of the formula (II)



(II)

with sulfonyl chloride or a halogenating agent to yield a compound of the formula (III)

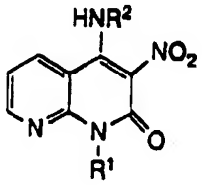


(III)

wherein L is sulfonyloxy or a halogen, which is further reacted with a compound of the formula (VII)

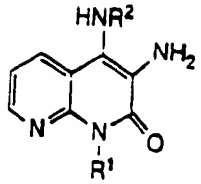
$$R^2NH_2 \qquad \text{(VII)}$$

to yield a compound of the formula (IV)



(IV)

which is reduced to a compound of the formula (V)

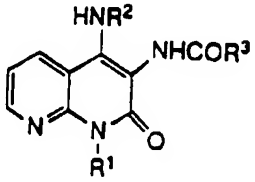


(V)

which is further reacted with a compound of the formula (IX)

$$R^3COOH \qquad (IX)$$

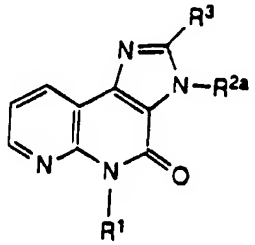
or a reactive derivative thereof to yield a compound of the formula (VI)



(VI)

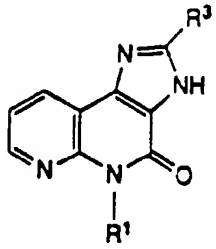
which is reacted in the presence of a cyclizing agent to the desired compound of the formula (Ia) which is optionally converted to a pharmaceutically acceptable salt thereof and wherein R^1, R^2 and R^3 in the compounds of the formulae II, III, IV, V, VI, VII and IX are as defined above.

2. A process for preparing an imidazonaphtyridine derivative of the formula (Ib),



(Ib)

wherein R^{2a} is R^2 as defined in claim 1 with the exception of hydrogen, which comprises reacting a compound of the formula (I-1),



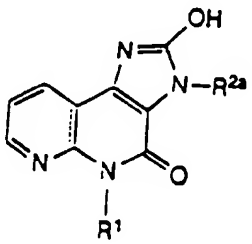
(I-1)

wherein R^1 and R^3 are as defined in claim 1, with a compound of the formula (X),

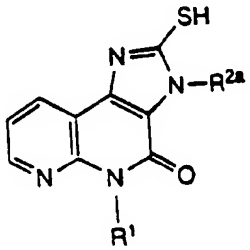
$$R^{2a}\text{-}L \qquad (X)$$

wherein R^{2a} is as defined above and L is as defined in claim 1 to yield the desired compound of the formula (Ib) which is optionally converted to a pharmaceutically acceptable salt thereof.

3. A process for preparing an imidazonaphtyridine derivative of the formula (Iba) which is represented by the formulae (Iba1) or (Iba2), respectively,



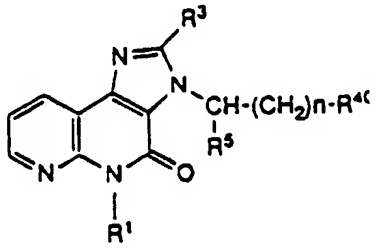
(Iba1)



(Iba2)

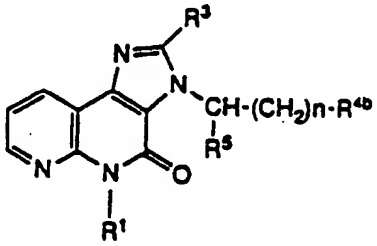
which comprises reacting a compound of the formula (V) as defined in claim 1 with carbonic acid dervative or a thiocarbonic acid derivative, respectively, to yield the desired compounds of the formula (Iba) which is optionally converted to a pharmaceutically acceptable salt thereof.

4. A process for preparing an imidazonaphtyridine derivative of the formula (Ic2),



(Ic2)

wherein R^1, R^3 and R^5 are as defined in cliam 1 and R^{4c} is NR^6R^7, wherein R^6 and R^7 are as defined in claim 1, ot morpholino, which comprises reacting a compound of the formula (Ic1)



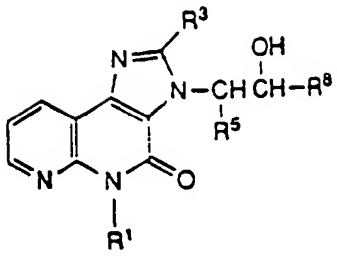
(Ic1)

wherein R^1, R^3 and R^5 are as defined above and R^{4b} is a halogen with a compound of the formula (XI),

$$R^{4c}\text{-}H \qquad \text{(XI)}$$

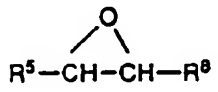
wherein R^{4c} is as defined above, to yield the desired compound of the formula (Ic2) which is optionally converted to a pharmaceutically acceptable salt thereof.

5. A process for preparing an imidazonaphtyridine derivative of the formula (Ic3),



(Ic3)

wherein R^1, R^3 and R^5 are as defined in claim 1 and R^8 is hydrogen or C_{1-7} alkyl, which comprises reacting a compound of the formula (I-1) as defined in claim 1 with a compound of the formula (XIII)



(XIII)

to yield the desired compound of the formula (Ic3), which is optionally converted to a pharmaceutically acceptable salt thereof.

6. The process according to claim 1, wherein R^2 is C_1-C_8 alkyl and R^3 is hydrogen.

7. The process according to claim 2, wherein R^{2a} is hydrogen, C_1-C_8 alkyl, C_2-C_6 alkenyl or $-C(R^5)H-(CH_2)_n-R^4$ (wherein R^4 represents substituted or unsubstituted phenyl or naphthyl, C_1-C_6 alkanoyloxy, (C_1-C_8 alkoxy)carbonyl, C_1-C_6 alkanoyl, substituted or unsubstituted pyridyl, or C_1-C_8 alkoxy; R^5 represents hydrogen; and n is 0 or 1); and R^3 represents hydrogen.

8. The process according to claim 7, wherein R^1 is C_1-C_8 alkyl or phenyl; and R^2 is hydrogen, C_1-C_8 alkyl or $-CH_2-R^4$ (wherein R^4 is phenyl or naphthyl, pyridyl or C_1-C_6 alkanoyl).

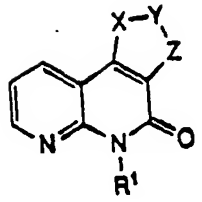
9. The process according to claim 1 for preparing a compound of the formula (I), namely

5-(n-butyl)-1-methyl-1H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one,
5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one, 3-ethyl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one,
5-phenyl-3-n-propyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one,
3-benzyl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one,
3-acetyl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one,
5-n-butyl-3-n-propyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one, and 5-phenyl-3-(3-pyridyl)methyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one.

10. The process according to any of claims 1 to 8, wherein said salt is an acid addition salt, a metal salt, an ammonium salt, an organic amine addition salt or an amino acid addition salt.

Claims for the following Contracting State : GR

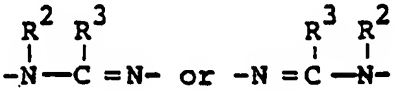
1. An imidazonaphthyridine derivative represented by formula (I):



(I)

wherein:

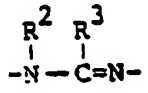
R^1 represents C_1-C_8 alkyl or substituted or unsubstituted phenyl or naphthyl; and
X-Y-Z represents



wherein R^2 represents hydrogen, C_1-C_8 alkyl, C_2-C_6 alkenyl, styryl or cinnamyl or $-C(R^5)H-(CH_2)_n-R^4$ (wherein R^4 represents substituted or unsubstituted phenyl or naphthyl, substituted or unsubstituted pyridyl, substituted or unsubstituted furyl, hydroxy-substituted C_1-C_8 alkyl, C_1-C_6 alkanoyloxy, morpholino, C_1-C_6 alkanoyl, carboxy, (C_1-C_8 alkoxy)carbonyl, C_3-C_8 cycloalkyl, hydroxy, C_1-C_8 alkoxy, halogen or NR^6R^7 wherein R^6 and R^7 independently represents hydrogen or C_1-C_8 alkyl; R^5 represents hydrogen, C_1-C_8 alkyl, or phenyl; and n represents an integer of 0 to 3); and R^3 represents hydrogen, mercapto, hydroxy, C_1-C_8 alkyl, or phenyl or naphthyl; whereby the substituents of phenyl, naphthyl, pyridyl and furyl may be one to three substituents selected from C_1-C_8 alkyl, C_1-C_8 alkoxy, nitro, (C_1-C_8 alkoxy)=carbonyl and halogen ;

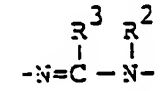
or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein X-Y-Z is



wherein R^2 is C_1-C_8 alkyl; and R^3 is hydrogen.

3. A compound according to claim 1, wherein X-Y-Z is



wherein R^2 is hydrogen, C_1-C_8 alkyl, C_2-C_6 alkenyl or $-C(R^5)H-(CH_2)_n-R^4$ (wherein R^4 represents substituted or unsubstituted phenyl or naphthyl, C_1-C_6 alkanoyloxy, (C_1-C_8 alkoxy)carbonyl, C_1-C_6 alkanoyl, substituted or unsubstituted pyridyl, or C_1-C_8 alkoxy; R^5 represents hydrogen; and n is 0 or 1); and R^3 represents hydrogen.

4. A compound according to claim 3, wherein R^1 is C_1-C_8 alkyl or phenyl; and R^2 is hydrogen, C_1-C_8 alkyl or $-CH_2-R^4$ (wherein R^4 is phenyl or naphthyl, pyridyl or C_1-C_6 alkanoyl).

5. A compound according to claim 1, namely

5-(n-butyl)-1-methyl-1H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one,
5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one, 3-ethyl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one,
5-phenyl-3-n-propyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one,
3-benzyl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one,
3-acetyl-5-phenyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one,

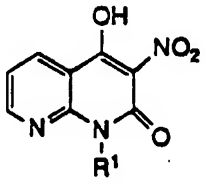
5-n-butyl-3-n-propyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one, or
5-phenyl-3-(-3-pyridyl)methyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one.

6. A compound according to any of claims 1 to 4, wherein said salt is an acid addition salt, a metal salt, an ammonium salt, an organic amine addition salt or an amino acid addition salt.

7. A process for preparing an imidazonaphtyridine derivative represented by the formula (Ia)

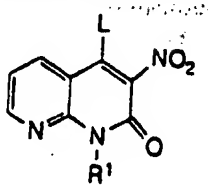
(Ia)

which comprises reacting a compound of the formula (II)



(II)

with sulfonyl chloride or a halogenating agent to yield a compound of the formula (III)

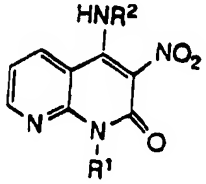


(III)

wherein L is sulfonyloxy or a halogen, which is further reacted with a compound of the formula (VII)

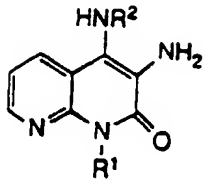
$$R^2NH_2 \qquad \text{(VII)}$$

to yield a compound of the formula (IV)



(IV)

which is reduced to a compound of the formula (V)

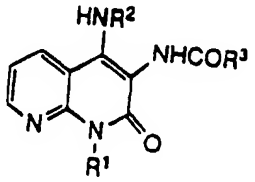


(V)

which is further reacted with a compound of the formula (IX)

$$R^3COOH \qquad (IX)$$

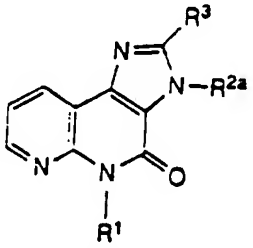
or a reactive derivative thereof to yield a compound of the formula (VI)



(VI)

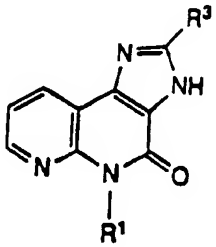
which is reacted in the presence of a cyclizing agent to the desired compound of the formula (Ia) which is optionally converted to a pharmaceutically acceptable salt thereof and wherein R^1, R^2 and R^3 in all of the above compounds are as defined in claim 1.

8. A process for preparing an imidazonaphtyridine derivative of the formula (Ib);



(Ib)

wherein R^{2a} is R^2 as defined in claim 1 with the exception of hydrogen, which comprises reacting a compound of the formula (I-1),



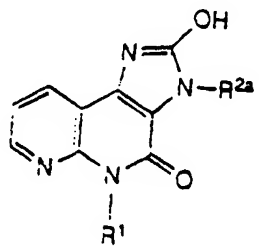
(I-1)

wherein R^1 and R^3 are as defined in claim 1, with a compound of the formula (X),

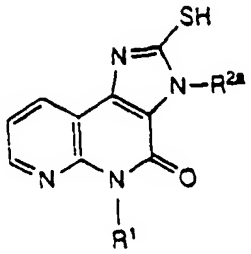
$$R^{2a}\text{-}L \qquad (X)$$

wherein R^{2a} is as defined above and L is as defined in claim 7 to yield the desired compound of the formula (Ib).

9. A process for preparing an imidazonaphtyridine derivative of the formula (Iba) which is represented by the formulae (Iba1) or (Iba2), respectively,



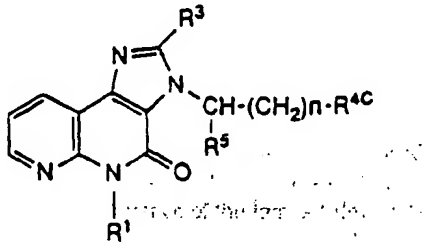
(Iba1)



(Iba2)

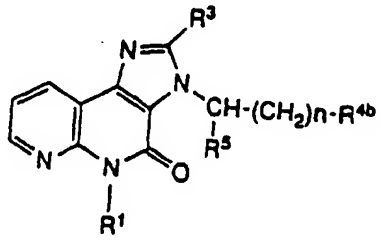
which comprises reacting a compound of the formula (V) as defined in claim 7 with carbonic acid dervative or a thiocarbonic acid derivative, respectively, to yield the desired compounds of the formula (Iba).

10. A process for preparing an imidazonaphtyridine derivative of the formula (Ic2),



(Ic2)

wherein R^1, R^3 and R^5 are as defined in claim 1 and R^{4c} is NR^6R^7, wherein R^6 and R^7 are as defined in claim 1, or morpholino, which comprises reacting a compound of the formula (Ic1)



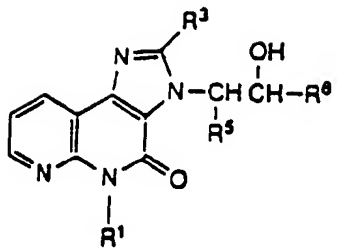
(Ic1)

wherein R^1, R^3 and R^5 are as defined above and R^{4b} is a halogen with a compound of the formula (XI),

$$R^{4c}\text{-}H \qquad \text{(XI)}$$

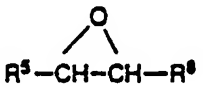
wherein R^{4c} is as defined above, to yield the desired compound of the formula (Ic2).

11. A process for preparing an imidazonaphtyridine derivative of the formula (Ic3),



(Ic3)

wherein R^1, R^3 and R^5 are as defined in claim 1 and R^8 is hydrogen or C_{1-7} alkyl, which comprises reacting a compound of the formula (I-1) as defined in claim 7 with a compound of the formula (XIII)



(XIII)

to yield the desired compound of the formula (Ic3).

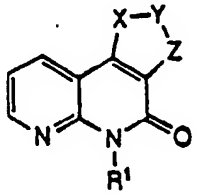
12. Use of a compound of the formula (I) as defined in any of claims 1 to 6 for the preparation of a pharmaceutical composition.

13. Use according to claim 12 wherein the composition has an anti-inflammatory, anti-allergic and/or broncho-dilative activity.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

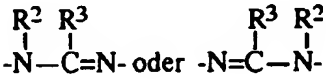
1. Imidazonaphthyridinderivat, das durch Formel (I) wiedergegeben wird:



(I)

in der

R^1 einen C_1-C_8-Alkylrest oder einen substituierten oder unsubstituierten Phenyl- oder Naphthylrest darstellt; und
X-Y-Z einen Rest

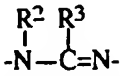


bedeutet, wobei R^2 ein Wasserstoffatom, einen C_1-C_8-Alkylrest, C_2-C_6-Alkenylrest, eine Styrylgruppe oder eine Cinnamylgruppe oder den Rest $-C(R^5)H-(CH_2)_n-R^4$ darstellt (wobei R^4 einen substituierten oder unsubstituierten Phenyl- oder Naphthylrest, einen substituierten oder unsubstituierten Pyridylrest, einen substituier-

ten oder unsubstituierten Furylrest, einen hydroxy-substituierten C_1-C_8-Alkylrest, einen C_1-C_6-Alkanoyloxyrest, eine Morpholinogruppe, einen C_1-C_6-Alkanoylrest, eine Carboxygruppe, einen (C_1-C_8-Alkoxy)carbonylrest, einen C_3-C_8-Cycloalkylrest, eine Hydroxygruppe, einen C_1-C_8-Alkoxyrest, ein Halogenatom oder einen Rest NR^6R^7 darstellt, wobei R^6 und R^7 jeweils unabhängig voneinander ein Wasserstoffatom oder einen C_1-C_8-Alkylrest bedeuten; R^5 ein Wasserstoffatom, einen C_1-C_8-Alkylrest oder eine Phenylgruppe darstellt; und n eine ganze Zahl von 0 bis 3 bedeutet); und R^3 ein Wasserstoffatom, eine Mercaptogruppe, eine Hydroxygruppe, einen C_1-C_8-Alkylrest, eine Phenylgruppe oder Naphtylgruppe darstellt; wobei es sich bei den Substituenten des Phenyl-, Naphthyl-, Pyridyl- und Furylrestes um ein bis drei Substituenten, ausgewählt aus C_1-C_8-Alkylresten, C_1-C_8-Alkoxyresten, Nitrogruppen, (C_1-C_8-Alkoxy)carbonylresten und Halogenatomen, handeln kann;

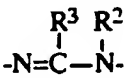
oder ein pharmazeutisch verträgliches Salz davon.

2. Verbindung nach Anspruch 1, wobei X-Y-Z einen Rest



bedeutet, in dem R^2 einen C_1-C_8-Alkylrest und R^3 ein Wasserstoffatom darstellt.

3. Verbindung nach Anspruch 1, wobei X-Y-Z einen Rest



bedeutet, in dem R^2 ein Wasserstoffatom, einen C_1-C_8-Alkylrest, C_2-C_6-Alkenylrest oder den Rest $-C(R^5)H-(CH_2)_n-R^4$ darstellt (wobei R^4 einen substituierten oder unsubstituierten Phenyl- oder Naphthylrest, einen C_1-C_6-Alkanoyloxyrest, einen (C_1-C_8-Alkoxy)carbonylrest, einen C_1-C_6-Alkanoylrest, einen substituierten oder unsubstituierten Pyridylrest oder einen C_1-C_8-Alkoxyrest darstellt; R^5 ein Wasserstoffatom darstellt; und n 0 oder 1 bedeutet); und R^3 ein Wasserstoffatom darstellt.

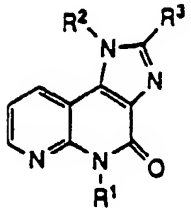
4. Verbindung nach Anspruch 3, wobei R^1 einen C_1-C_8-Alkylrest oder einen Phenylrest darstellt; und R^2 ein Wasserstoffatom, einen C_1-C_8-Alkylrest oder den Rest $-CH_2-R^4$ bedeutet (wobei R^4 einen Phenyl- oder Naphthylrest, einen Pyridylrest oder einen C_1-C_6-Alkanoylrest darstellt).

5. Verbindung nach Anspruch 1, nämlich

5-(n-Butyl)-1-methyl-1H-imidazo[4,5-c][1,8]napthyndin-4(5H)-on,
5-Phenyl-3H-imidazo[4,5-c][1,8]napthyridin-4(5H)-on
3-Ethyl-5-phenyl-3H-imidazo[4,5-c][1,8]napthyridin-4(5H)-on,
5-Phenyl-3-n-propyl-3H-imidazo[4,5-c][1,8]napthyridin-4(5H)-on,
3-Benzyl-5-phenyl-3H-imidazo[4,5-c][1,8]napthyridin-4(5H)-on,
3-Acetyl-5-phenyl-3H-imidazo[4,5-c][1,8]napthyridin-4(5H)-on,
5-n-Butyl-3-n-propyl-3H-imidazo[4,5-c][1,8]napthyridin-4(5H)-on oder
5-Phenyl-3-(3-pyridyl)methyl-3H-imidazo[4,5-c][1,8]napthyridin4(5H)-on.

6. Verbindung nach einem der Ansprüche 1 bis 4, wobei es sich bei dem Salz um ein Säureadditionssalz, ein Metallsalz, ein Ammoniumsalz, ein Additionssalz mit einem organischen Amin oder um ein Additionsalz mit einer Aminosäure handelt.

7. Verfahren zur Herstellung eines durch die Formel (Ia) wiedergegebenen Imidazonaphthyridinderivats,

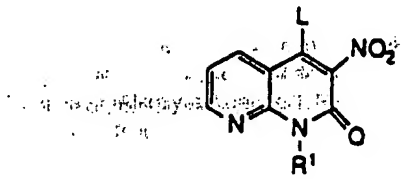


(Ia)

umfassend die Umsetzung einer Verbindung der Formel (II)

(II)

mit Sulfonylchlorid oder einem Halogenierungsmittel, wobei eine Verbindung der Formel (III) erhalten wird,

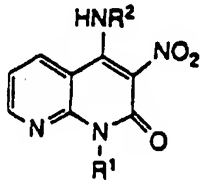


(III)

in der L eine Sulfonyloxygruppe oder ein Halogenatom darstellt, die weiter mit einer Verbindung der Formel (VII) umgesetzt wird,

$$R^2NH_2 \qquad \text{(VII)}$$

wobei eine Verbindung der Formel (IV) erhalten wird,



(IV)

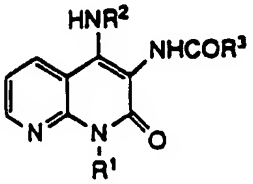
die zu einer Verbindung der Formel (V) reduziert wird,

(V)

die weiter mit einer Verbindung der Formel (IX) oder einem reaktiven Derivat davon umgesetzt wird,

$$R^3COOH \qquad (IX)$$

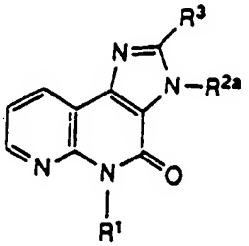
wobei eine Verbindung der Formel (VI) erhalten wird,



(VI)

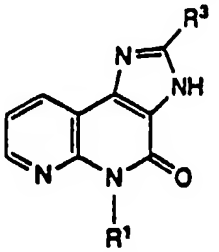
die in Gegenwart eines Cyclisierungsmittels zu der gewünschten Verbindung der Formel (Ia) umgesetzt wird, die gegebenenfalls in ein pharmazeutisch verträgliches Salz davon überführt wird, und in der R^1, R^2 und R^3 in allen vorstehenden Verbindungen wie in Anspruch 1 definiert sind.

8. Verfahren zur Herstellung eines durch die Formel (Ib) wiedergegebenen Imidazonaphthyridinderivats



(Ib)

in der R^{2a} den Rest R^2 darstellt, wie er in Anspruch 1 definiert ist, mit Ausnahme des Wasserstoffatoms, umfassend die Umsetzung einer Verbindung der Formel (I-1),



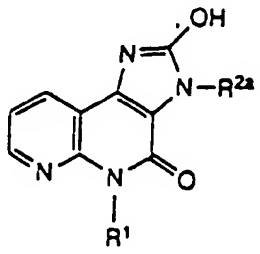
(I-1)

in der R^1 und R^3 wie in Anspruch 1 definiert sind, mit einer Verbindung der Formel (X),

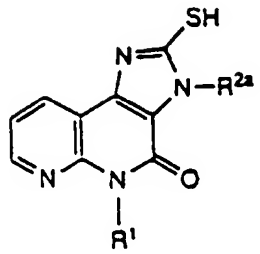
$$R^{2a}\text{-}L \qquad (X)$$

in der R^{2a} wie vorstehend und L wie in Anspruch 7 definiert sind, wobei die gewünschte Verbindung der Formel (Ib) erhalten wird.

9. Verfahren zur Herstellung eines Imidazonaphthyridinderivats der Formel (Iba), das durch die Formeln (Iba1) beziehungsweise (Iba2) wiedergegeben wird,



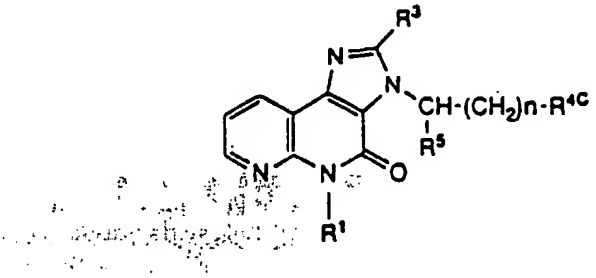
(Iba1)



(Iba2)

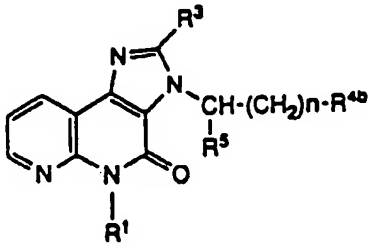
umfassend die Umsetzung einer Verbindung der Formel (V), wie sie in Anspruch 7 definiert wurde, mit einem Kohlensäurederivat beziehungsweise einem Thiokohlensäurederivat, wobei die gewünschten Verbindungen der Formel (Iba) erhalten werden.

10. Verfahren zur Herstellung eines Imidazonaphthyridinderivats der Formel (Ic2),



(Ic2)

in der R^1, R^3 und R^5 wie in Anspruch 1 definiert sind und R^{4c} den Rest NR^6R^7, in dem R^6 und R^7 wein Anspruch 1 definiert sind, oder eine Morpholinogruppe darstellt, umfassend die Umsetzung einer Verbindung der Formel (Ic1),



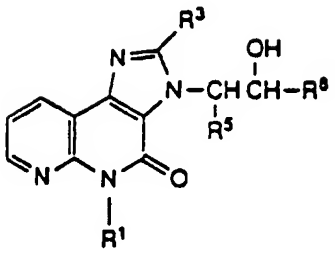
(Ic1)

in der R^1 , R^3 und R^5 wie vorstehend definiert sind und R^{4b} ein Halogenatom darstellt, mit einer Verbindung der Formel (XI),

$$R^{4c}\text{-}H \qquad \text{(XI)}$$

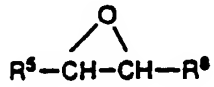
in der R^{4c} wie vorstehend definiert ist, wobei die gewünschte Verbindung der Formel (Ic2) erhalten wird.

11. Verfahren zur Herstellung eines Imidazonaphthyridinderivats der Formel (Ic3),



(Ic3)

in der R^1, R^3 und R^5 wie in Anspruch 1 definiert sind und R^8 ein Wasserstoffatom oder einen C_{1-7}-Alkylrest darstellt, umfassend die Umsetzung einer Verbindung der Formel (I-1), wie sie in Anspruch 7 definiert wurde, mit einer Verbindung der Formel (XIII),



(XIII)

wobei die gewünschte Verbindung der Formel (Ic3) erhalten wird.

12. Verwendung einer Verbindung der Formel (I), wie sie in einem der Ansprüche 1 bis 6 definiert wurde, zur Herstellung eines Arzneimittels.

13. Verwendung nach Anspruch 12, wobei das Mittel eine entzündungshemmende, antiallergische und/oder bronchodilative Wirkung besitzt.

14. Arzneimittel, enthaltend eine in einem der Ansprüche 1 bis 6 definierte Verbindung der Formel (I), deren pharmazeutisch verträgliche Salze oder deren physiologisch funktionelle Derivate, die im Körper in diese überführbar sind, und gegebenenfalls einen pharmazeutisch verträglichen Träger und/oder Verdünnungsmittel.

15. Mittel nach Anspruch 14, das eine entzündungshemmende, antiallergische und/oder bronchodilative Wirkung aufweist.

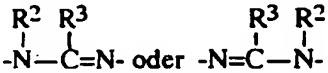
Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zur Herstellung eines durch die Formel (I) wiedergegebenen Imidazonaphthyridinderivats

(I)

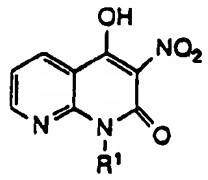
in der

R^1 einen C_1-C_8-Alkylrest oder einen substituierten oder unsubstituierten Phenyl- oder Naphthylrest darstellt; und
X-Y-Z einen Rest



bedeutet, wobei R^2 ein Wasserstoffatom, einen C_1-C_8-Alkylrest, C_2-C_6-Alkenylrest, eine Styrylgruppe oder

eine Cinnamylgruppe oder den Rest -C(R^5)H-(CH_2)$_n$-R^4 darstellt (wobei R^4 einen substituierten oder unsubstituierten Phenyl- oder Naphthylrest, einen substituierten oder unsubstituierten Pyridylrest, einen substituierten oder unsubstituierten Furylrest, einen hydroxy-substituierten C_1-C_8-Alkylrest, einen C_1-C_6-Alkanoyloxyrest, eine Morpholinogruppe, einen C_1-C_6-Alkanoylrest, eine Carboxygruppe, einen (C_1-C_8-Alkoxy)carbonylrest, einen C_3-C_8-Cycloalkylrest, eine Hydroxygruppe, einen C_1-C_8-Alkoxyrest, ein Halogenatom oder einen Rest NR^6R^7 darstellt, wobei R^6 und R^7 jeweils unabhängig voneinander ein Wasserstoffatom oder einen C_1-C_8-Alkylrest bedeuten; R^5 ein Wasserstoffatom, einen C_1-C_8-Alkylrest oder eine Phenylgruppe darstellt; und n eine ganze Zahl von 0 bis 3 bedeutet); und R^3 ein Wasserstoffatom, eine Mercaptogruppe, eine Hydroxygruppe, einen C_1-C_8-Alkylrest, eine Phenylgruppe oder Naphthylgruppe darstellt; wobei es sich bei den Substituenten des Phenyl-, Naphthyl-, Pyridyl- und Furylrestes um ein bis drei Substituenten, ausgewählt aus C_1-C_8-Alkylresten, C_1-C_8-Alkoxyresten, Nitrogruppen (C_1-C_8-Alkoxy)carbonylresten und Halogenatomen, handeln kann; oder eines pharmazeutisch verträgliches Salz davon; umfassend
die Umsetzung einer Verbindung der Formel (II)



(II)

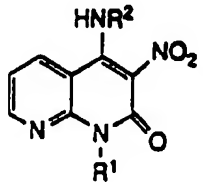
mit Sulfonylchlorid oder einem Halogenierungsmittel, wobei eine Verbindung der Formel (III) erhalten wird,

(III)

in der L eine Sulfonyloxygruppe oder ein Halogenatom darstellt, die weiter mit einer Verbindung der Formel (VII) umgesetzt wird,

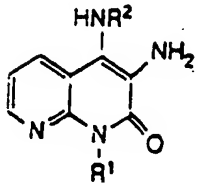
$$R^2NH_2 \qquad \text{(VII)}$$

wobei eine Verbindung der Formel (IV) erhalten wird,



(IV)

die zu einer Verbindung der Formel (V) reduziert wird,

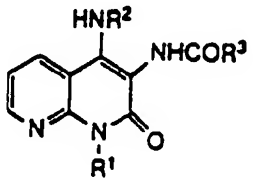


(V)

die weiter mit einer Verbindung der Formel (IX) oder einem reaktiven Derivat davon umgesetzt wird,

$$R^3COOH \qquad (IX)$$

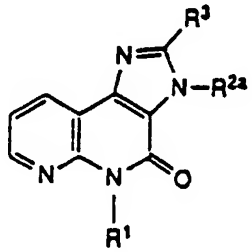
wobei eine Verbindung der Formel (VI) erhalten wird



(VI)

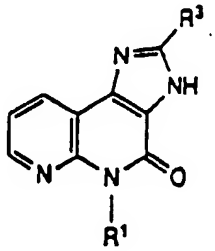
die in Gegenwart eines Cyclisierungsmittels zu der gewünschten Verbindung der Formel (Ia) umgesetzt wird, die gegebenenfalls in ein pharmazeutisch verträgliches Salz davon überführt wird, und in der R^1, R^2 und R^3 in den Verbindungen der Formeln II, III, IV, V, VI, VII und IX wie vorstehend definiert sind.

2. Verfahren zur Herstellung eines durch die Formel (Ib) wiedergegebenen Imidazonaphthyridinderivats,



(Ib)

in der R^{2a} den Rest R^2 darstellt, wie er in Anspruch 1 definiert ist, mit Ausnahme des Wasserstoffatoms, umfassend die Umsetzung einer Verbindung der Formel (I-1),



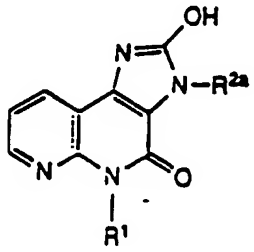
(I-1)

in der R^1 und R^3 wie in Anspruch 1 definiert sind, mit einer Verbindung der Formel (X),

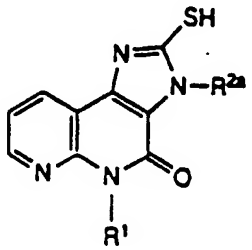
$$R^{2a}\text{-}L \qquad (X)$$

in der R^{2a} wie vorstehend und L wie in Anspruch 1 definiert sind, wobei die gewünschte Verbindung der Formel (Ib) erhalten wird, die gegebenenfalls in ein pharmazeutisch verträgliches Salz davon überführt wird.

3. Verfahren zur Herstellung eines Imidazonaphthyridinderivats der Formel (Iba), das durch die Formeln (Iba1) beziehungsweise (Iba2) wiedergegeben wird,



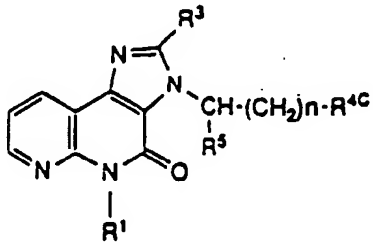
(Iba1)



(Iba2)

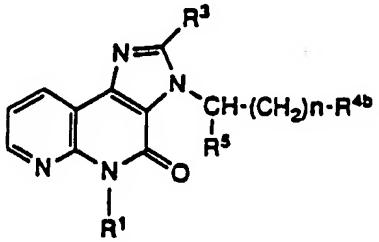
umfassend die Umsetzung einer Verbindung der Formel (V), wie sie in Anspruch 1 definiert wurde, mit einem Kohlensäurederivat beziehungsweise einem Thiokohlensäurederivat, wobei die gewünschten Verbindungen der Formel (Iba) erhalten werden, die gegebenenfalls in ein pharmazeutisch verträgliches Salz davon überführt werden.

4. Verfahren zur Herstellung eines Imidazonaphthyridinderivats der Formel (Ic2),



(Ic2)

wobei R^1, R^3 und R^5 wie in Anspruch 1 definiert sind und R^{4c} den Rest NR^6R^7, in dem R^6 und R^7 wie in Anspruch 1 definiert sind, oder eine Morpholinogruppe darstellt, umfassend die Umsetzung einer Verbindung der Formel (Ic1),



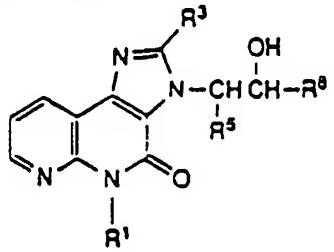
(Ic1)

in der R^1, R^3 und R^5 wie vorstehend definiert sind und R^{4b} ein Halogenatom darstellt, mit einer Verbindung der Formel (XI),

$$R^{4c}\text{-}H \qquad (XI)$$

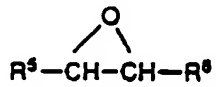
in der R^{4c} wie vorstehend definert ist, wobei die gewünschte Verbindung der Formel (Ic2) erhalten wird, die gegebenenfalls in ein pharmazeutisch verträgliches Salz davon überführt wird.

5. Verfahren zur Herstellung eines Imidazonaphthyridinderivats der Formel (Ic3),



(Ic3)

in der R^1, R^3 und R^5 wie in Anspruch 1 definiert sind und R^8 ein Wasserstoffatom oder einen C_{1-7}-Alkylrest darstellt, umfassend die Umsetzung einer Verbindung der Formel (I-1), wie sie in Anspruch 1 definiert wurde, mit einer Verbindung der Formel (XIII),



(XIII)

wobei die gewünschte Verbindung der Formel (Ic3) erhalten wird, die gegebenenfalls in ein pharmazeutisch verträgliches Salz davon überführt wird.

6. Verfahren nach Anspruch 1, wobei R^2 einen C_1-C_8-Alkylrest und R^3 ein Wasserstoffatom darstellen.

7. Verfahren nach Anspruch 2, wobei R^{2a} ein Wasserstoffatom, einen C_1-C_8-Alkylrest, C_2-C_6-Alkenylrest oder den Rest $-C(R^5)H-(CH_2)_n-R^4$ darstellt (wobei R^4 einen substituierten oder unsubstituierten Phenyl- oder Naphthylrest, einen C_1-C_6-Alkanoyloxyrest, einen (C_1-C_8-Alkoxy)carbonylrest, einen C_1-C_6-Alkanoylrest, einen substituierten oder unsubstituierten Pyridylrest oder einen C_1-C_8-Alkoxyrest darstellt, R^5 ein Wasserstoffatom darstellt; und n 0 oder 1 bedeutet); und R^3 ein Wasserstoffatom darstellt.

8. Verfahren nach Anspruch 7, wobei R^1 einen C_1-C_8-Alkylrest oder einen Phenylrest darstellt, R^2 ein Wasserstoffatom, einen C_1-C_8-Alkylrest oder einen Rest $-CH_2-R^4$ darstellt (wobei R^4 einen Phenyl- oder Naphthylrest, einen Pyridylrest oder einen C_1-C_6-Alkanoylrest darstellt).

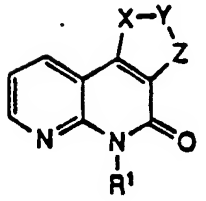
9. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung der Formel (I), nämlich

5-(n-Butyl)-1-methyl-1H-imidazo[4,5-c][1,8]napthyridin-4(5H)-on,
5-Phenyl-3H-imidazo[4,5-c][1,8]napthyridin-4(5H)-on,
3-Ethyl-5-phenyl-3H-imidazo[4,5-c][1,8]napthyridin-4(5H)-on,
5-Phenyl-3-n-propyl-3H-imidazo[4,5-c][1,8]napthyridin-4(5H)-on,
3-Benzyl-5-phenyl-3H-imidazo[4,5-c][1,8]napthyridin-4(5H)-on,
3-Acetyl-5-phenyl-3H-imidazo[4,5-c][1,8]napthyridin-4(5H)-on,
5-n-Butyl-3-n-propyl-3H-imidazo[4,5-c][1,8]napthyridin-4(5H)-on und
5-Phenyl-3-(3-pyridyl)methyl-3H-imidazo[4,5-c][1,8]napthyridin-4(5H)-on.

10. Verfahren nach einem der Ansprüche 1 bis 8, wobei es sich bei dem Salz um ein Säureadditionssalz, ein Metallsalz, ein Ammoniumsalz, ein Additionssalz mit einem organischen Amin oder um ein Additionsalz mit einer Aminosäure handelt.

Patentansprüche für folgenden Vertragsstaat : GR

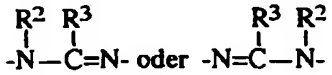
1. Imidazonaphthyridinderivat, das durch Formel (I) wiedergegeben wird:



(I)

in der

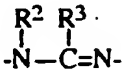
R^1 einen C_1-C_8-Alkylrest oder einen substituierten oder unsubstituierten Phenyl- oder Naphthylrest darstellt; und
X-Y-Z einen Rest



bedeutet, wobei R^2 ein Wasserstoffatom, einen C_1-C_8-Alkylrest, C_2-C_6-Alkenylrest, eine Styrylgruppe oder eine Cinnamylgruppe oder den Rest $-C(R^5)H-(CH_2)_n-R^4$ darstellt (wobei R^4 einen substituierten oder unsubstituierten Phenyl- oder Naphthylrest, einen substituierten oder unsubstituierten Pyridylrest, einen substituierten oder unsubstituierten Furylrest, einen hydroxy-substituierten C_1-C_8-Alkylrest, einen C_1-C_6-Alkanoyloxyrest, eine Morpholinogruppe, einen C_1-C_6-Alkanoylrest, eine Carboxygruppe, einen (C_1-C_8-Alkoxy)carbonylrest, einen C_3-C_8-Cycloalkylrest, eine Hydroxygruppe, einen C_1-C_8-Alkoxyrest, ein Halogenatom oder einen Rest NR^6R^7 darstellt, in dem R^6 und R^7 jeweils unabhängig voneinander ein Wasserstoffatom oder einen C_1-C_8-Alkylrest bedeuten; R^5 ein Wasserstoffatom, einen C_1-C_8-Alkylrest oder eine Phenylgruppe darstellt; und n eine ganze Zahl von 0 bis 3 bedeutet); und R^3 ein Wasserstoffatom, eine Mercaptogruppe, eine Hydroxygruppe, einen C_1-C_8-Alkylrest, eine Phenyl- oder Naphtylgruppe darstellt; wobei es sich bei den Substituenten des Phenyl-, Naphthyl-, Pyridyl- und Furylrestes um ein bis drei Substituenten, ausgewählt aus C_1-C_8-Alkylresten, C_1-C_8-Alkoxyresten, Nitrogruppen, (C_1-C_8-Alkoxy)carbonylresten und Halogenatomen, handeln kann;

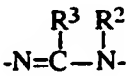
oder ein pharmazeutisch verträgliches Salz davon.

2. Verbindung nach Anspruch 1, wobei X-Y-Z einen Rest



bedeutet, in dem R^2 einen C_1-C_8-Alkylrest und R^3 ein Wasserstoffatom darstellt.

3. Verbindung nach Anspruch 1, wobei X-Y-Z einen Rest



bedeutet, in dem R^2 ein Wasserstoffatom, einen C_1-C_8-Alkylrest, C_2-C_6-Alkenylrest oder den Rest $-C(R^5)H-(CH_2)_n-R^4$ darstellt (wobei R^4 einen substituierten oder unsubstituierten Phenyl- oder Naphthylrest, einen C_1-C_6-Alkanoyloxyrest, einen (C_1-C_8-Alkoxy)carbonylrest, einen C_1-C_6-Alkanoylrest, einen substituierten oder unsubstituierten Pyridylrest oder einen C_1-C_8-Alkoxyrest darstellt; R^5 ein Wasserstoffatom darstellt; und n 0 oder 1 bedeutet); und R^3 ein Wasserstoffatom darstellt.

4. Verbindung nach Anspruch 3, wobei R^1 einen C_1-C_8-Alkylrest oder einen Phenylrest darstellt; R^2 ein Wasserstoffatom, einen C_1-C_8-Alkylrest oder den Rest $-CH_2-R^4$ bedeutet (wobei R^4 einen Phenyl- oder Naphthylrest, einen Pyridylrest oder einen C_1-C_6-Alkanoylrest darstellt).

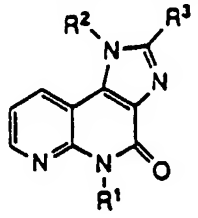
5. Verbindung nach Anspruch 1, nämlich

5-(n-Butyl)-1-methyl-1H-imidazo[4,5-c][1,8]napthyridin-4(5H)-on,

5-Phenyl-3H-imidazo[4,5-c][1,8]napthyridin-4(5H)-on,
3-Ethyl-5-phenyl-3H-imidazo[4,5-c][1,8]napthyridin-4(5H)-on,
5-Phenyl-3-n-propyl-3H-imidazo[4,5-c][1,8]napthyridin-4(5H)-on,
3-Benzyl-5-phenyl-3H-imidazo[4,5-c][1,8]napthyridin-4(5H)-on,
3-Acetyl-5-phenyl-3H-imidazo[4,5-c][1,8]napthyridin-4(5H)-on,
5-n-Butyl-3-n-propyl-3H-imidazo[4,5-c][1,8]napthyridin-4(5H)-on oder
5-Phenyl-3-(3-pyridyl)methyl-3H-imidazo[4,5-c][1,8]napthyridin-4(5H)-on.

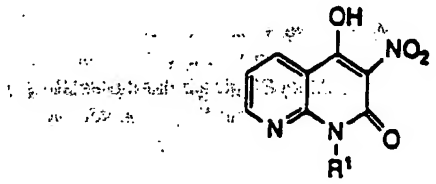
6. Verbindung nach einem der Ansprüche 1 bis 4, wobei es sich bei dem Salz um ein Säureadditionssalz, ein Metallsalz, ein Ammoniumsalz, ein Additionssalz mit einem organischen Amin oder um ein Additionsalz mit einer Aminosäure handelt.

7. Verfahren zur Herstellung eines durch die Formel (Ia) wiedergegebenen Imidazonaphthyridinderivats,



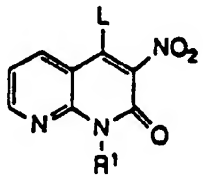
(Ia)

umfassend die Umsetzung einer Verbindung der Formel (II)



(II)

mit Sulfonylchlorid oder einem Halogenierungsmittel, wobei eine Verbindung der Formel (III) erhalten wird



(III)

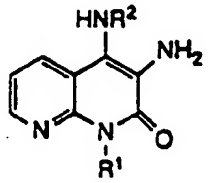
in der L eine Sulfonyloxygruppe oder ein Halogenatom darstellt, die weiter mit einer Verbindung der Formel (VII) umgesetzt wird

$$R^2NH_2 \qquad \text{(VII)}$$

wobei eine Verbindung der Formel (IV) erhalten wird,

(IV)

die zu einer Verbindung der Formel (V) reduziert wird,

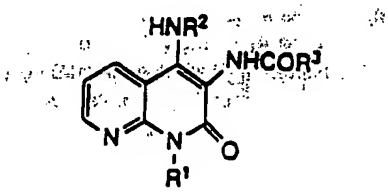


(V)

die weiter mit einer Verbindung der Formel (IX) oder einem reaktiven Derivat davon umgesetzt wird,

$$R^3COOH \qquad (IX)$$

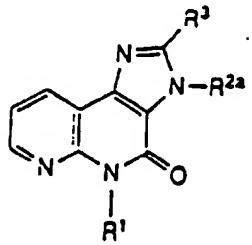
wobei eine Verbindung der Formel (VI) erhalten wird,



(VI)

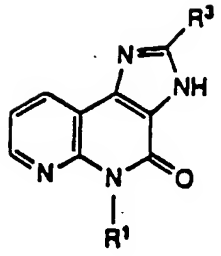
die in Gegenwart eines Cyclisierungsmittels zu der gewünschten Verbindung der Formel (Ia) umgesetzt wird, die gegebenenfalls in ein pharmazeutisch verträgliches Salz davon überführt wird, und in der R^1, R^2 und R^3 in allen vorstehenden Verbindungen wie in Anspruch 1 definiert sind.

8. Verfahren zur Herstellung eines durch die Formel (Ib) wiedergegebenen Imidazonaphthyridinderivats,



(Ib)

in der R^{2a} den Rest R^2 darstellt, wie er in Anspruch 1 definiert ist, mit Ausnahme Wasserstoffatoms, umfassend die Umsetzung einer Verbindung der Formel (I-1),



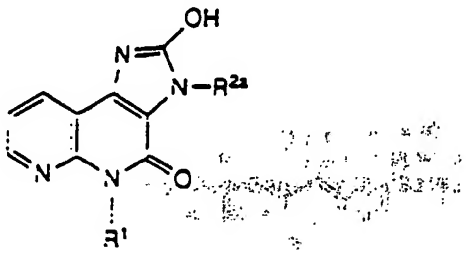
(I-1)

in der R^1 und R^3 wie in Anspruch 1 definiert sind, mit einer Verbindung der Formel (X),

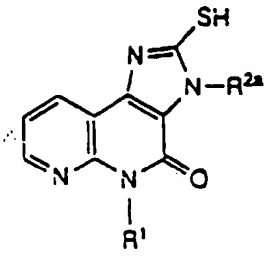
$$R^{2a}\text{-}L \qquad (X)$$

in der R^{2a} wie vorstehend und L wie in Anspruch 7 definiert sind, wobei die gewünschte Verbindung der Formel (Ib) erhalten wird.

9. Verfahren zur Herstellung eines Imidazonaphthyridinderivats der Formel (Iba), das durch die Formeln (Iba1) beziehungsweise (Iba2) wiedergegeben wird,



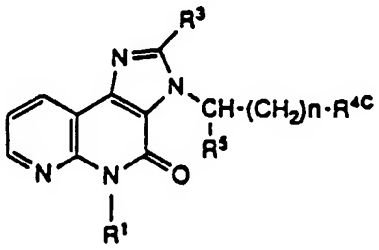
(Iba1)



(Iba2)

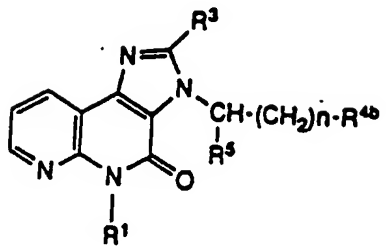
umfassend die Umsetzung einer Verbindung der Formel (V), wie sie in Anspruch 7 definiert wurde, mit einem Kohlensäurederivat beziehungsweise einem Thiokohlensäurederivat, wobei die gewünschten Verbindungen der Formel (Iba) erhalten werden.

10. Verfahren zur Herstellung eines Imidazonaphthyridinderivats der Formel (Ic2),



(Ic2)

in der R^1, R^3 und R^5 wie in Anspruch 1 definiert sind und R^{4c} den Rest NR^6R^7, in dem R^6 und R^7 wie in Anspruch 1 definiert sind, oder eine Morpholinogruppe darstellt, umfassend die Umsetzung einer Verbindung der Formel (Ic1),



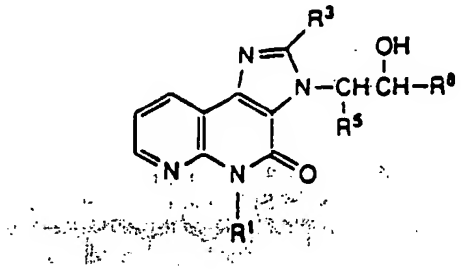
(Ic1)

in der R^1, R^3 und R^5 wie vorstehend definiert sind und R^{4b} ein Halogenatom darstellt, mit einer Verbindung der Formel (XI) umfaßt,

$$R^{4c}\text{-}H \qquad (XI)$$

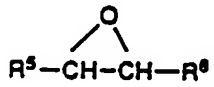
in der R^{4c} wie vorstehend definiert ist, wobei die gewünschte Verbindung der Formel (Ic2) erhalten wird.

11. Verfahren zur Herstellung eines Imidazonaphthyridinderivats der Formel (Ic3),



(Ic3)

in der R^1, R^3 und R^5 wie in Anspruch 1 definiert sind und R^8 ein Wasserstoffatom oder einen $C_{1\text{-}7}$-Alkylrest darstellt, umfassend die Umsetzung einer Verbindung der Formel (I-1), wie sie in Anspruch 7 definiert wurde, mit einer Verbindung der Formel (XIII),



(XIII)

wobei die gewünschte Verbindung der Formel (Ic3) erhalten wird.

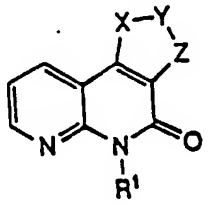
12. Verwendung einer Verbindung der Formel (I), wie sie in einem der Ansprüche 1 bis 6 definiert wurde, zur Herstellung eines Arzneimittels.

13. Verwendung nach Anspruch 12, wobei das Mittel eine entzündungshemmende, antiallergische und/oder bronchodilative Wirkung besitzt.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

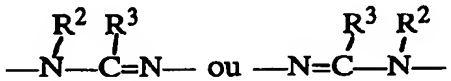
1. Dérivé d'imidazonaphtyridine, représenté par la formule (I) :



(I)

dans laquelle

R^1 représente un groupe alkyle en C_{1-8} ou un groupe phényle ou naphtyle portant ou non des substituants, et X-Y-Z représente

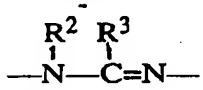


où R^2 représente un atome d'hydrogène, un groupe alkyle en C_{1-8}, alcényle en C_{2-6}, styryle ou cinnamyle, ou un groupe de formule

$$-C(R^5)H-(CH_2)_n-R^4$$

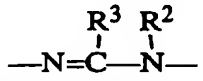
dans laquelle R^4 représente un groupe phényle ou naphtyle portant ou non des substituants, pyridyle portant ou non des substituants, furyle portant ou non des substituants, alkyle en C_{1-8} à substituant(s) hydroxy, alcanoyloxy en C_{1-6}, morpholino, alcanoyle en C_{1-6}, carboxy, (alcoxy en C_{1-8})-carbonyle, cycloalkyle en C_{3-8}, hydroxy ou alcoxy en C_{1-8}, un atome d'halogène ou encore un groupe $-NR^6R^7$ où R^6 et R^7 représentent chacun, indépendamment, un atome d'hydrogène ou un groupe alkyle en C_{1-8}, R^5 représente un atome d'hydrogène ou un groupe alkyle en C_{1-8} ou phényle, et n représente un nombre entier valant de 0 à 3,
et R^3 représente un atome d'hydrogène ou un groupe mercapto, hydroxy, alkyle en C_{1-8}, phényle ou naphtyle ;
les substituants des groupes phényle, naphtyle, pyridyle et furyle pouvant être au nombre d'un à trois substituants choisis parmi les groupes alkyle en C_{1-8}, alcoxy en C_{1-8}, nitro et (alcoxy en C_{1-8})-carbonyle et les atomes d'halogène ;
ou sel, admissible en pharmacie, d'un tel dérivé.

2. Composé conforme à la revendication 1, dans lequel X-Y-Z représente



où R^2 représente un groupe alkyle en C_{1-8} et R^3 représente un atome d'hydrogène.

3. Composé conforme à la revendication 1, dans lequel X-Y-Z représente



où R^2 représente un atome d'hydrogène, un groupe alkyle en C_{1-8} ou alcényle en C_{2-6} ou un groupe de formule

$$-C(R^5)H-(CH_2)_n-R^4$$

dans laquelle R^4 représente un groupe phényle ou naphtyle portant ou non des substituants, alcanoyloxy en C_{1-6}, (alcoxy en C_{1-8})-carbonyle, alcanoyle en C_{1-6}, pyridyle portant ou non des substituants, ou alcoxy en C_{1-8}, R^5 représente un atome d'hydrogène et n vaut 0 ou 1, et R^3 représente un atome d'hydrogène.

4. Composé conforme à la revendication 3, dans lequel R^1 représente un groupe alkyle en C_{1-8} ou phényle, et R^2

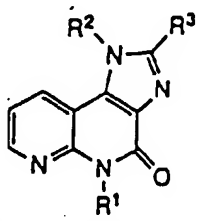
représente un atome d'hydrogène, un groupe alkyle en C_{1-8} ou un groupe de formule $-CH_2-R^4$ dans laquelle R^4 représente un groupe phényle, naphtyle, pyridyle ou alcanoyle en C_{1-6}.

5. Composé conforme à la revendication 1, à savoir :

5-(n-butyl)-1-méthyl-1H-imidazo[4,5-c][1,8]naphtyridine-4(5H)-one,
5-phényl-3H-imidazo[4,5-c][1,8]naphtyridine-4(5H)-one,
3-éthyl-5-phényl-3H-imidazo[4,5-c][1,8]naphtyridine-4(5H)-one,
5-phényl-3-n-propyl-3H-imidazo[4,5-c][1,8]naphtyridine-4(5H)-one,
3-benzyl-5-phényl-3H-imidazo[4,5-c][1,8] naphtyridine-4(5H)-one,
3-acétyl-5-phényl-3H-imidazo[4,5-c][1,8]naphtyridine-4(5H)-one,
5-n-butyl-3-n-propyl-3H-imidazo[4,5-c][1,8] naphtyridine-4(5H)-one,
ou 5-phényl-3-(3-pyridyl)méthyl-3H-imidazo[4,5-c][1,8]naphtyridine-4(5H)-one.

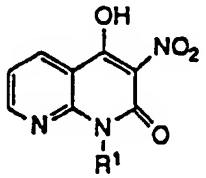
6. Composé conforme à l'une des revendications 1 à 4, dans lequel ledit sel est un sel d'addition d'acide, un sel de métal, un sel d'ammonium, un sel d'addition d'amine organique, ou un sel d'addition d'acide aminé.

7. Procédé de préparation d'un dérivé d'imidazonaphtyridine représenté par la formule (Ia) :



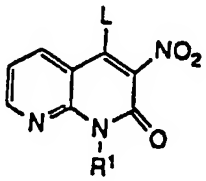
(Ia)

lequel procédé comporte le fait de faire réagir un composé de formule (II)



(II)

avec du chlorure de sulfonyle ou un agent d'halogénation, pour obtenir un composé de formule (III)

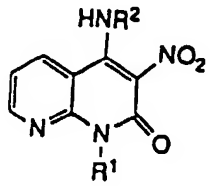


(III)

dans laquelle L représente un groupe sulfonyloxy ou un atome d'halogène,
composé que l'on fait ensuite réagir avec un composé de formule (VII)

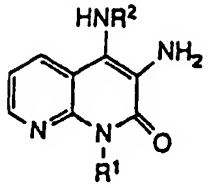
$$R^2NH_2 \qquad \text{(VII)}$$

pour obtenir un composé de formule (IV)



(IV)

que l'on réduit en un composé de formule (V)

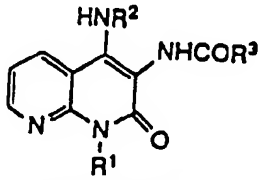


(V)

composé que l'on fait ensuite réagir avec un composé de formule (IX)

$$R^3COOH \qquad (IX)$$

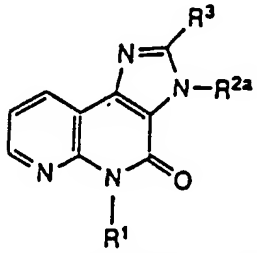
ou avec un dérivé réactif d'un tel composé, ce qui donne un composé de formule (VI)



(VI)

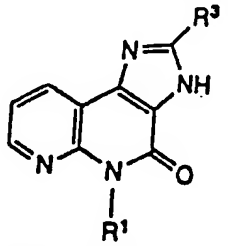
que l'on fait réagir, en présence d'un agent de cyclisation, pour obtenir le composé voulu, de formule (Ia), que l'on transforme éventuellement en l'un de ses sels admissibles en pharmacie,
R^1, R^2 et R^3 ayant, dans tous les composés représentés ci-dessus, les significations indiquées dans la revendication 1.

8. Procédé de préparation d'un dérivé d'imidazonaphtyridine représenté par la formule (Ib) :



(Ib)

dans laquelle R^{2a} a les significations indiquées pour R^2 dans la revendication 1, sauf celle d'un atome d'hydrogène, lequel procédé comporte le fait de faire réagir un composé de formule (I-1) :



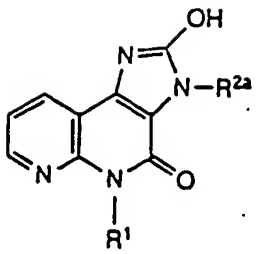
(I-1)

dans laquelle R^1 et R^3 ont les significations indiquées dans la revendication 1,
avec un composé de formule (X) :

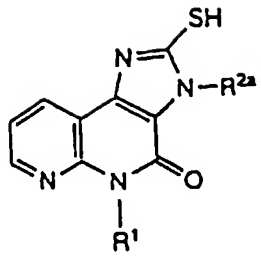
$$R^{2a}\text{-}L \qquad (X)$$

dans laquelle R^{2a} a la signification indiquée ci-dessus et L a la signification indiquée dans la revendication 7, pour obtenir le composé voulu, de formule (Ib).

9. Procédé de préparation d'un dérivé d'imidazonaphtyridine de formule (Iba), représenté par l'une des formules (Iba1) et (Iba2) :



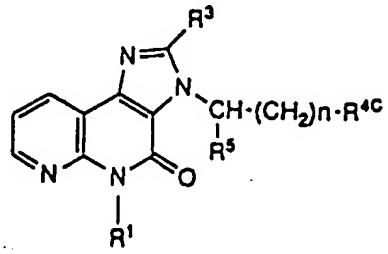
(Iba1)



(Iba2)

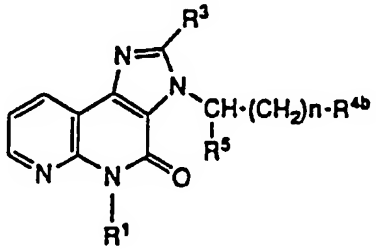
lequel procédé comporte le fait de faire réagir un composé de formule (V), indiquée dans la revendication 7, respectivement avec un dérivé de l'acide carbonique ou de l'acide thiocarbonique, pour obtenir les composés voulus, de formule (Iba).

10. Procédé de préparation d'un dérivé d'imidazonaphtyridine de formule (Ic2) :



(Ic2)

dans laquelle R^1, R^3 et R^5 ont les significations indiquées dans la revendication 1 et R^{4c} représente un groupe morpholino ou un groupe de formule $-NR^6R^7$ où R^6 et R^7 ont les significations indiquées dans la revendication 1, lequel procédé comporte le fait de faire réagir un composé de formule (Ic1) :



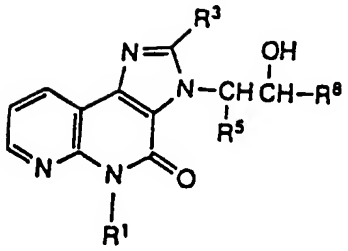
(Ic1)

dans laquelle R^1, R^3 et R^5 ont les significations indiquées ci-dessus et R^{4b} représente un atome d'halogène, avec un composé de formule (XI) :

$$R^{4c}\text{-}H \qquad \text{(XI)}$$

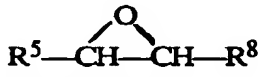
dans laquelle R^{4c} a la signification indiquée ci-dessus,
pour obtenir le composé voulu, de formule (Ic2).

11. Procédé de préparation d'un dérivé d'imidazonaphtyridine de formule (Ic3) :



(Ic3)

dans laquelle R^1, R^3 et R^5 ont les significations indiquées dans la revendication 1 et R^8 représente un atome d'hydrogène ou un groupe alkyle en C_{1-7},
lequel procédé comporte le fait de faire réagir un composé de formule (I-1), indiquée dans la revendication 7, avec un composé de formule (XIII):



(XIII)

pour obtenir le composé voulu, de formule (Ic3).

12. Emploi d'un composé de formule (I), conforme à l'une des revendications 1 à 6, dans la préparation d'une composition pharmaceutique.

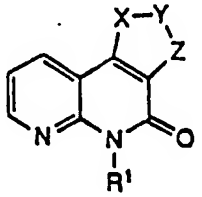
13. Emploi conforme à la revendication 12, la composition ainsi préparée ayant une activité anti-inflammatoire, anti-allergique et/ou bronchodilatatrice.

14. Composition pharmaceutique contenant un composé de formule (I), conforme à l'une des revendications 1 à 6, ou un sel ou un dérivé physiologiquement actif d'un tel composé, admissible en pharmacie et qui peut être transformé en un tel composé dans le corps, et le cas échéant, un diluant et/ou un véhicule admissible en pharmacie.

15. Composition conforme à la revendication 14, qui présente une activité anti-inflammatoire, anti-allergique et/ou bronchodilatatrice.

Revendications pour l'Etat contractant suivant : ES

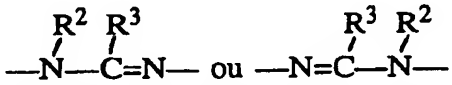
1. Procédé de préparation d'un dérivé d'imidazonaphtyridine, représenté par la formule (I):



(I)

dans laquelle

R^1 représente un groupe alkyle en C_{1-8} ou un groupe phényle ou naphtyle portant ou non des substituants, et X-Y-Z représente



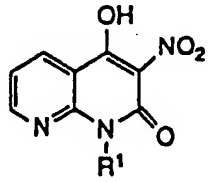
où R^2 représente un atome d'hydrogène, un groupe alkyle en C_{1-8}, alcényle en C_{2-6} styryle ou cinnamyle, ou un groupe de formule

$$-C(R^5)H-(CH_2)_n-R^4$$

dans laquelle R^4 représente un groupe phényle ou naphtyle portant ou non des substituants, pyridyle portant

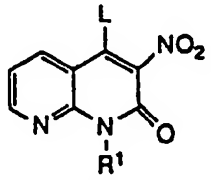
ou non des substituants, furyle portant ou non des substituants, alkyle en C_{1-8} à substituant(s) hydroxy, alcanoyloxy en C_{1-6}, morpholino, alcanoyle en C_{1-6}, carboxy, (alcoxy en C_{1-8})-carbonyle, cycloalkyle en C_{3-8}, hydroxy ou alcoxy en C_{1-8}, un atome d'halogène ou encore un groupe $-NR^6R^7$ où R^6 et R^7 représentent chacun, indépendamment, un atome d'hydrogène ou un groupe alkyle en C_{1-8}, R^5 représente un atome d'hydrogène ou un groupe alkyle en C_{1-8} ou phényle, et n représente un nombre entier valant de 0 à 3,
et R^3 représente un atome d'hydrogène ou un groupe mercapto, hydroxy, alkyle en C_{1-8}, phényle ou naphtyle ; les substituants des groupes phényle, naphtyle, pyridyle et furyle pouvant être au nombre d'un à trois substituants choisis parmi les groupes alkyle en C_{1-8}, alcoxy en C_{1-8}, nitro et (alcoxy en C_{1-8})-carbonyle et les atomes d'halogène ;
ou d'un sel, admissible en pharmacie, d'un tel dérivé,

lequel procédé comporte le fait de faire réagir un composé de formule (II)



(II)

avec du chlorure de sulfonyle ou un agent d'halogénation, pour obtenir un composé de formule (III)

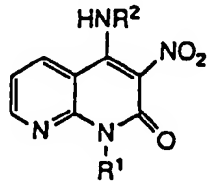


(III)

dans laquelle L représente un groupe sulfonyloxy ou un atome d'halogène;
composé que l'on fait ensuite réagir avec un composé de formule (VII)

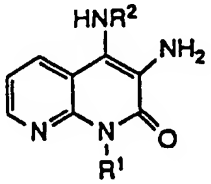
$$R^2NH_2 \qquad \text{(VII)}$$

pour obtenir un composé de formule (IV)



(IV)

que l'on réduit en un composé de formule (V)

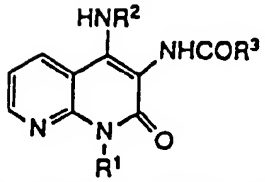


(V)

composé que l'on fait ensuite réagir avec un composé de formule (IX)

$$R^3COOH \qquad \text{(IX)}$$

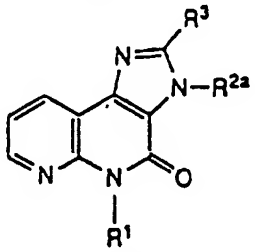
ou avec un dérivé réactif d'un tel composé, ce qui donne un composé de formule (VI)



(VI)

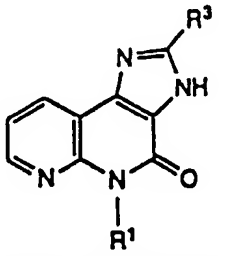
que l'on fait réagir, en présence d'un agent de cyclisation, pour obtenir le composé voulu, de formule (Ia), que l'on transforme éventuellement en l'un de ses sels admissibles en pharmacie,
R^1, R^2 et R^3 ayant, dans les composés de formules II, III, IV, V, VI, VII et IX, les significations indiquées plus haut.

2. Procédé de préparation d'un dérivé d'imidazonaphtyridine représenté par la formule (Ib) :



(Ib)

dans laquelle R^{2a} a les significations indiquées pour R^2 dans la revendication 1, sauf celle d'un atome d'hydrogène, lequel procédé comporte le fait de faire réagir un composé de formule (I-1) :



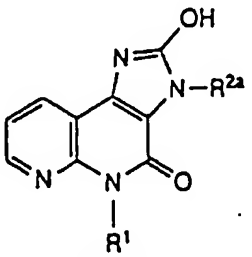
(I-1)

dans laquelle R^1 et R^3 ont les significations indiquées dans la revendication 1,
avec un composé de formule (X) :

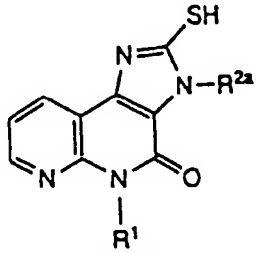
$$R^{2a}\text{-}L \qquad (X)$$

dans laquelle R^{2a} a la signification indiquée ci-dessus et L a la signification indiquée dans la revendication 1, pour obtenir le composé voulu, de formule (Ib), que l'on transforme éventuellement en l'un de ses sels admissibles en pharmacie.

3. Procédé de préparation d'un dérivé d'imidazonaphtyridine de formule (Iba), représenté par l'une des formules (Iba1) et (Iba2) :



(Iba1)

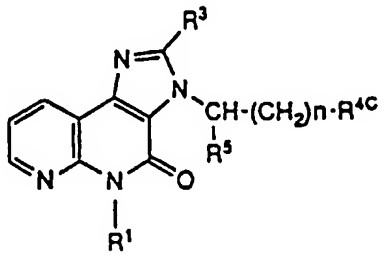


(Iba2)

lequel procédé comporte le fait de faire réagir un composé de formule (V), indiquée dans la revendication 1,

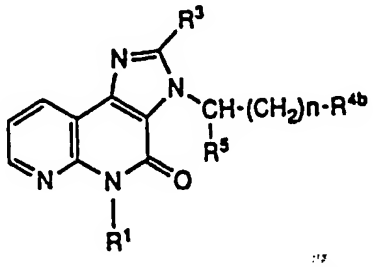
respectivement avec un dérivé de l'acide carbonique ou de l'acide thiocarbonique, pour obtenir les composés voulus, de formule (Iba), que l'on transforme éventuellement en l'un de leurs sels admissibles en pharmacie.

4. Procédé de préparation d'un dérivé d'imidazonaphtyridine de formule (Ic2) :



(Ic2)

dans laquelle R^1, R^3 et R^5 ont les significations indiquées dans la revendication 1 et R^{4c} représente un groupe morpholino ou un groupe de formule $-NR^6R^7$ où R^6 et R^7 ont les significations indiquées dans la revendication 1, lequel procédé comporte le fait de faire réagir un composé de formule (Ic1) :



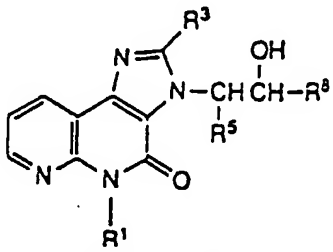
(Ic1)

dans laquelle R^1, R^3 et R^5 ont les significations indiquées ci-dessus et R^{4b} représente un atome d'halogène, avec un composé de formule (XI) :

$$R^{4c}\text{-H} \qquad \text{(XI)}$$

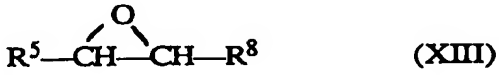
dans laquelle R^{4c} a la signification indiquée ci-dessus,
pour obtenir le composé voulu, de formule (Ic2), que l'on transforme éventuellement en l'un de ses sels admissibles en pharmacie.

5. Procédé de préparation d'un dérivé d'imidazonaphtyridine de formule (Ic3) :



(Ic3)

dans laquelle R^1, R^3 et R^5 ont les significations indiquées dans la revendication 1 et R^8 représente un atome d'hydrogène ou un groupe alkyle en C_{1-7},
lequel procédé comporte le fait de faire réagir un composé de formule (I-1), indiquée dans la revendication 1, avec un composé de formule (XIII) :



(XIII)

pour obtenir le composé voulu, de formule (Ic3), que l'on transforme éventuellement en l'un de ses sels admissibles en pharmacie.

6. Procédé conforme à la revendication 1, dans lequel R^2 représente un groupe alkyle en C_{1-8} et R^3 représente un atome d'hydrogène.

7. Procédé conforme à la revendication 2, dans lequel R^{2a} représente un atome d'hydrogène, un groupe alkyle en C_{1-8} ou alcényle en C_{2-6}, ou un groupe de formule

$$-C(R^5)H-(CH_2)_n-R^4$$

dans laquelle R^4 représente un groupe phényle ou naphtyle portant ou non des substituants, alcanoyloxy en C_{1-6}, (alcoxy en C_{1-8})-carbonyle, alcanoyle en C_{1-6}, pyridyle portant ou non des substituants, ou alcoxy en C_{1-8}, R^5 représente un atome d'hydrogène et n vaut 0 ou 1,
et R^3 représente un atome d'hydrogène.

8. Procédé conforme à la revendication 7, dans lequel R^1 représente un groupe alkyle en C_{1-8} ou phényle, et R^2 représente un atome d'hydrogène, un groupe alkyle en C_{1-8} ou un groupe de formule $-CH_2-R^4$ dans laquelle R^4 représente un groupe phényle, naphtyle, pyridyle ou alcanoyle en C_{1-6}.

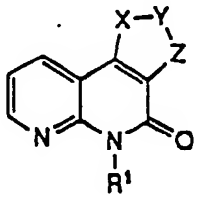
9. Procédé, conforme à la revendication 1, de préparation d'un composé de formule (I), à savoir :

5-(n-butyl)-1-méthyl-1H-imidazo[4,5-c][1,8]naphtyridine-4(5H)-one,
5-phényl-3H-imidazo[4,5-c][1,8]naphtyridine-4(5H)-one,
3-éthyl-5-phényl-3H-imidazo[4,5-c][1,8]naphtyridine-4(5H)-one,
5-phényl-3-n-propyl-3H-imidazo[4,5-c][1,8]naphtyridine-4(5H)-one,
3-benzyl-5-phényl-3H-imidazo[4,5-c][1,8]naphtyridine-4(5H)-one,
3-acétyl-5-phényl-3H-imidazo[4,5-c][1,8]naphtyridine-4(5H)-one,
5-n-butyl-3-n-propyl-3H-imidazo[4,5-c][1,8]naphtyridine-4(5H)-one,
ou 5-phényl-3-(3-pyridyl)méthyl-3H-imidazo[4,5-c][1,8]naphtyridine-4(5H)-one.

10. Procédé conforme à l'une des revendications 1 à 8, dans lequel ledit sel est un sel d'addition d'acide, un sel de métal, un sel d'ammonium, un sel d'addition d'amine organique, ou un sel d'addition d'acide aminé.

Revendications pour l'Etat contractant suivant : GR

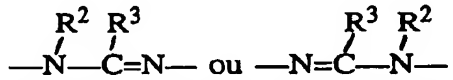
1. Dérivé d'imidazonaphtyridine, représenté par la formule (I):



(I)

dans laquelle

R^1 représente un groupe alkyle en C_{1-8} ou un groupe phényle ou naphtyle portant ou non des substituants, et X-Y-Z représente



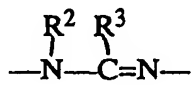
où R^2 représente un atome d'hydrogène, un groupe alkyle en C_{1-8}, alcényle en C_{2-6} styryle ou cinnamyle, ou un groupe de formule

$$-C(R^5)H-(CH_2)_n-R^4$$

dans laquelle R^4 représente un groupe phényle ou naphtyle portant ou non des substituants, pyridyle portant ou non des substituants, furyle portant ou non des substituants, alkyle en C_{1-8} à substituant(s) hydroxy, alcanoyloxy en C_{1-6}, morpholino, alcanoyle en C_{1-6}, carboxy, (alcoxy en C_{1-8})-carbonyle, cycloalkyle en C_{3-8}, hy-

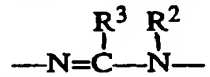
droxy ou alcoxy en C_{1-8}, un atome d'halogène ou encore un groupe $-NR^6R^7$ où R^6 et R^7 représentent chacun, indépendamment, un atome d'hydrogène ou un groupe alkyle en C_{1-8}, R^5 représente un atome d'hydrogène ou un groupe alkyle en C_{1-8} ou phényle, et n représente un nombre entier valant de 0 à 3,
et R^3 représente un atome d'hydrogène ou un groupe mercapto, hydroxy, alkyle en C_{1-8}, phényle ou naphtyle ;
les substituants des groupes phényle, naphtyle, pyridyle et furyle pouvant être au nombre d'un à trois substituants choisis parmi les groupes alkyle en C_{1-8}, alcoxy en C_{1-8}, nitro et (alcoxy en C_{1-8})-carbonyle et les atomes d'halogène ;
ou sel, admissible en pharmacie, d'un tel dérivé.

2. Composé conforme à la revendication 1, dans lequel X-Y-Z représente



où R^2 représente un groupe alkyle en C_{1-8} et R^3 représente un atome d'hydrogène.

3. Composé conforme à la revendication 1, dans lequel X-Y-Z représente



où R^2 représente un atome d'hydrogène, un groupe alkyle en C_{1-8} ou alcényle en C_{2-6}, ou un groupe de formule

$$-C(R^5)H-(CH_2)_n-R^4$$

dans laquelle R^4 représente un groupe phényle ou naphtyle portant ou non des substituants, alcanoyloxy en C_{1-6}, (alcoxy en C_{1-8})-carbonyle, alcanoyle en C_{1-6}, pyridyle portant ou non des substituants, ou alcoxy en C_{1-8}, R^5 représente un atome d'hydrogène et n vaut 0 ou 1,
et R^3 représente un atome d'hydrogène.

4. Composé conforme à la revendication 3, dans lequel R^1 représente un groupe alkyle en C_{1-8} ou phényle, et R^2 représente un atome d'hydrogène, un groupe alkyle en C_{1-8} ou un groupe de formule $-CH_2-R^4$ dans laquelle R^4 représente un groupe phényle, naphtyle, pyridyle ou alcanoyle en C_{1-6}.

5. Composé conforme à la revendication 1, à savoir :

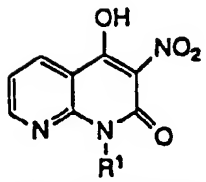
5-(n-butyl)-1-méthyl-1H-imidazo[4,5-c][1,8]naphtyridine-4(5H)-one,
5-phényl-3H-imidazo[4,5-c][1,8]naphtyridine-4(5H)-one,
3-éthyl-5-phényl-3H-imidazo[4,5-c][1,8]naphtyridine-4(5H)-one,
5-phényl-3-n-propyl-3H-imidazo[4,5-c][1,8]naphtyridine-4(5H)-one,
3-benzyl-5-phényl-3H-imidazo[4,5-c][1,8]naphtyridine-4(5H)-one,
3-acétyl-5-phényl-3H-imidazo[4,5-c][1,8]naphtyridine-4(5H)-one,
5-n-butyl-3-n-propyl-3H-imidazo[4,5-c][1,8]naphtyridine-4(5H)-one,
ou 5-phényl-3-(3-pyridyl)méthyl-3H-imidazo[4,5-c][1,8]naphtyridine-4(5H)-one.

6. Composé conforme à l'une des revendications 1 à 4, dans lequel ledit sel est un sel d'addition d'acide, un sel de métal, un sel d'ammonium, un sel d'addition d'amine organique, ou un sel d'addition d'acide aminé.

7. Procédé de préparation d'un dérivé d'imidazonaphtyridine représenté par la formule (Ia):

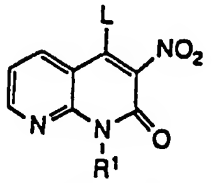
(Ia)

lequel procédé comporte le fait de faire réagir un composé de formule (II)



(II)

avec du chlorure de sulfonyle ou un agent d'halogénation, pour obtenir un composé de formule (III)

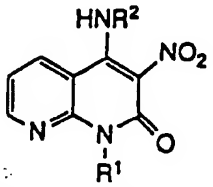


(III)

dans laquelle L représente un groupe sulfonyloxy ou un atome d'halogène,
composé que l'on fait ensuite réagir avec un composé de formule (VII)

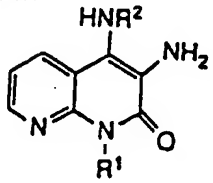
$$R^2NH_2 \qquad \text{(VII)}$$

pour obtenir un composé de formule (IV)



(IV)

que l'on réduit en un composé de formule (V)

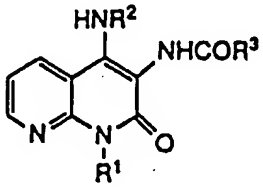


(V)

composé que l'on fait ensuite réagir avec un composé de formule (IX)

$$R^3COOH \qquad \text{(IX)}$$

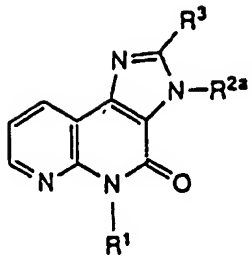
ou avec un dérivé réactif d'un tel composé, ce qui donne un composé de formule (VI)



(VI)

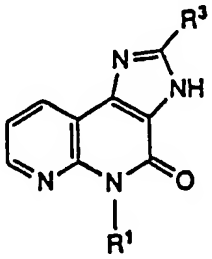
que l'on fait réagir, en présence d'un agent de cyclisation, pour obtenir le composé voulu, de formule (Ia), que l'on transforme éventuellement en l'un de ses sels admissibles en pharmacie,
R^1, R^2 et R^3 ayant, dans tous les composés représentés ci-dessus, les significations indiquées dans la revendication 1.

8. Procédé de préparation d'un dérivé d'imidazonaphtyridine représenté par la formule (Ib) :



(Ib)

dans laquelle R^{2a} a les significations indiquées pour R^2 dans la revendication 1, sauf celle d'un atome d'hydrogène, lequel procédé comporte le fait de faire réagir un composé de formule (I-1) :



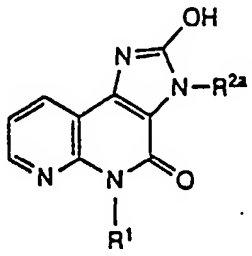
(I-1)

dans laquelle R^1 et R^3 ont les significations indiquées dans la revendication 1, avec un composé de formule (X) :

$$R^{2a}\text{-}L \qquad (X)$$

dans laquelle R^{2a} a la signification indiquée ci-dessus et L a la signification indiquée dans la revendication 7, pour obtenir le composé voulu, de formule (Ib).

9. Procédé de préparation d'un dérivé d'imidazonaphtyridine de formule (Iba), représenté par l'une des formules (Iba1) et (Iba2) :

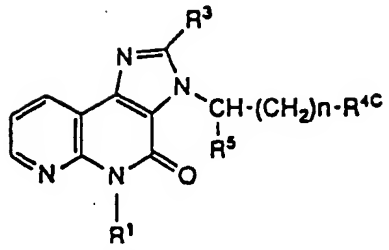


(Iba1)

(Iba2)

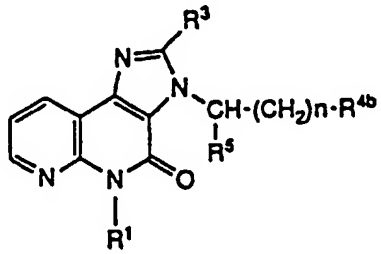
lequel procédé comporte le fait de faire réagir un composé de formule (V), indiquée dans la revendication 7, respectivement avec un dérivé de l'acide carbonique ou de l'acide thiocarbonique, pour obtenir les composés voulus, de formule (Iba).

10. Procédé de préparation d'un dérivé d'imidazonaphtyridine de formule (Ic2) :



(Ic2)

dans laquelle R^1, R^3 et R^5 ont les significations indiquées dans la revendication 1 et R^{4c} représente un groupe morpholino ou un groupe de formule $-NR^6R^7$ où R^6 et R^7 ont les significations indiquées dans la revendication 1, lequel procédé comporte le fait de faire réagir un composé de formule (Ic1) :



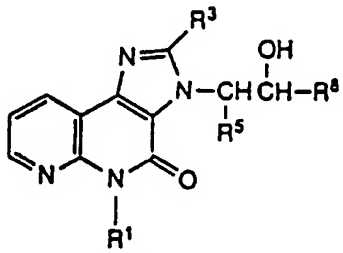
(Ic1)

dans laquelle R^1, R^3 et R^5 ont les significations indiquées ci-dessus et R^{4b} représente un atome d'halogène, avec un composé de formule (XI) :

$$R^{4c}\text{-}H \qquad \text{(XI)}$$

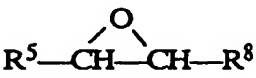
dans laquelle R^{4c} a la signification indiquée ci-dessus,
pour obtenir le composé voulu, de formule (Ic2).

11. Procédé de préparation d'un dérivé d'imidazonaphtyridine de formule (Ic3) :



(Ic3)

dans laquelle R^1, R^3 et R^5 ont les significations indiquées dans la revendication 1 et R^8 représente un atome d'hydrogène ou un groupe alkyle en C_{1-7},
lequel procédé comporte le fait de faire réagir un composé de formule (I-1), indiquée dans la revendication 7, avec un composé de formule (XIII):



(XIII)

pour obtenir le composé voulu, de formule (Ic3).

12. Emploi d'un composé de formule (I), conforme à l'une des revendications 1 à 6, dans la préparation d'une composition pharmaceutique.

13. Emploi conforme à la revendication 12, la composition ainsi préparée ayant une activité anti-inflammatoire, anti-allergique et/ou bronchodilatatrice.

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(54) Dihydro-isoquinoline derivates

Dihydro-Isoquinolinderivate

Dérivés de dihydro-isoquinoleino

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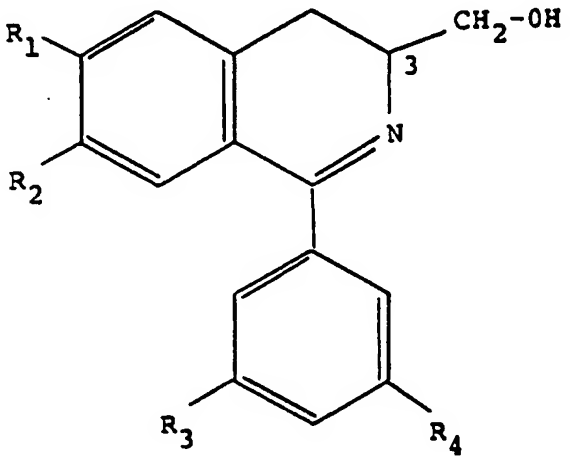
Description

The present invention relates to novel dihydro-isoquinoline derivatives having pharmaceutical utility, processes for their production, pharmaceutical compositions comprising them and their use as pharmaceuticals.

FR-A-2 625 743 discloses isoquinoline and dihydro-isoquinoline derivatives having bronchodilatator activity

More particularly the present invention provides a compound of formula I



(I)

wherein

R_1 to R_4 are each independently C_{1-4}alkoxy,

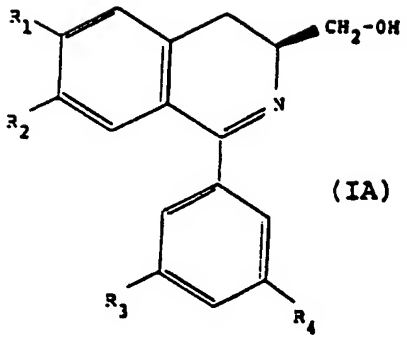
or physiologically-hydrolysable and -acceptable ester thereof, or acid addition salt of such a compound or ester.

In the compounds of formula I, alkoxy groups and moieties may be branched or straight chain. Suitably they are straight chain. Most preferably R_1 to R_4 are each methoxy.

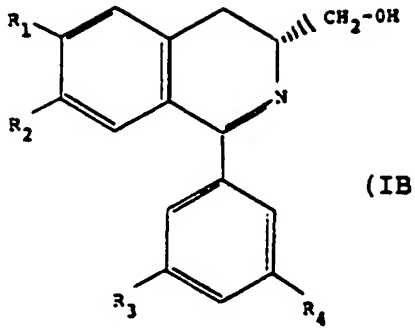
By "physiologically-hydrolysable and -acceptable ester" as used herein is meant an ester in which the hydroxy group at the 3-position is esterified and which is hydrolysable under physiological conditions to yield an acid which is itself physiologically tolerable at dosages to be administered. The term is thus to be understood as defining regular pro-drug forms. Examples of such esters include for example the 3-acetates, as well as -benzoates of the formula I compounds.

Compounds of formula I and their esters as aforesaid exist in both free and acid addition salt form. Suitable pharmaceutically acceptable acid addition salt forms for use in accordance with the present invention include, for example, the hydrochloride, oxalate and fumarate salts.

The 3-position carbon atom of compounds of formula I is asymmetric. The compounds of the invention thus exist in enantiomeric form, i.e. as optically active antipodes having the [3S] or [3R] configuration. In relation to formula I these may be represented as follows:



(IA)



(IB)

Formula IA represents the [3S]-enantiomer and formula IB the [3R]-enantiomer. Unless otherwise specified, the present invention is to be understood as embracing both individual [3S] and [3R] enantiomers as well as mixtures, e.g. racemic mixtures, of the compounds of formula I, their esters and acid addition salts as aforesaid.

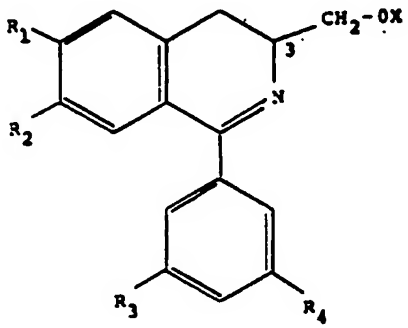
In general, for pharmaceutical use in accordance with the present invention, the [3S] enantiomer of the compounds of the invention will be preferred. Thus the preferred compound of formula I is [3S] 3,4-dihydro-6,7-dimethoxy-1-(3,5-dimethoxyphenyl)-3-hydroxymethyl-isoquinoline [Formula IA: R_1 to R_4 all = CH_3O-].

Accordingly, in a preferred embodiment, the present invention provides a compound of formula I as hereinbefore defined in [3S] enantiomeric form, for example, in pure or substantially pure [3S] enantiomeric form (e.g. comprising 80% or more, preferably 90% or more, especially 95 or 98% or more of the pure [3S] enantiomer), or physiologically-hydrolysable or -acceptable ester thereof or acid addition salt of such a compound or ester.

Individual enantiomers of compounds of the invention may be obtained in conventional manner, e.g. employing optically active starting materials, or by separation of initially obtained racemates for example as hereinafter described.

In a further aspect the present invention also provides a method for the production of compounds of the invention which method comprises:

a) for the production of a compound of formula I as defined above, removing the protecting group from a compound of formula I as defined above in 3-hydroxy protected form, i.e. from a compound of formula II



(II)

wherein R_1 to R_4 have the meanings given for formula I and X is a hydroxy protecting group; or

b) for the production of a physiologically-hydrolysable and -acceptable ester of a compound of formula I as defined above, esterifying a compound of formula I as defined above; and

recovering the obtained compound of formula I or ester thereof in free or acid addition salt form.

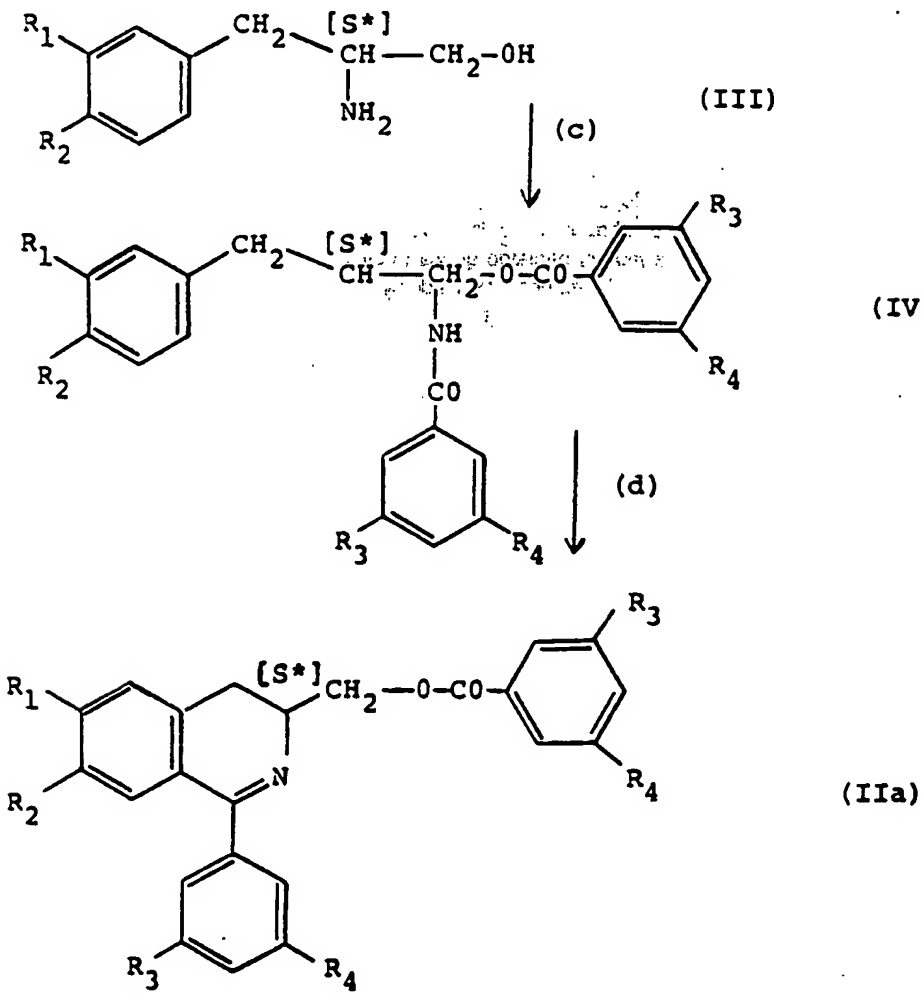
Process step (a) may be performed in accordance with methods known and practiced in the art for the removal of hydroxy-protecting groups. Suitable hydroxy protecting groups as X include any of those known and commonly employed in the art, for example benzoyl or substituted benzoyl groups, in particular 3,5-dialkoxy benzoyl groups in which the alkoxy moieties correspond to R_3 and R_4 of formula I.

Such groups are for example suitably removed by hydrolytic cleavage, e.g. in the presence of aqueous lithium hydroxide and a lower alkanol, e.g. at temperatures of from 0° to 50°C.

Esterification in accordance with process step (b) may also be conducted in accordance with standard procedures, e.g. by reaction of a compound of formula I with an appropriate acid halide or anhydride in the presence of a base, for example an amine or alkali metal carbonate. The reaction is suitably carried out in an inert solvent or diluent, e.g. at a temperature of from 0° to 120°C, under an inert atmosphere.

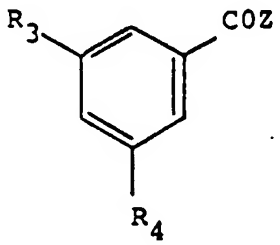
Where the product obtained by the above processes comprises a mixture of enantiomers, e.g. racemic mixture, the individual enantiomers may, if desired, be separated by conventional procedures, e.g. resolution by crystallisation using optically active acids or chromatographic separation using a chiral stationary phase, to yield the [3S] or [3R] enantiomer in pure or substantially pure form. Alternatively the pure enantiomers may be prepared directly from the corresponding optically pure starting material, e.g. a compound of formula II in [3S] enantiomeric form, for example as described in the accompanying example.

The hydroxy protected derivatives of formula II employed as starting materials for process step (a) are also new and form part of the invention. They may be prepared in accordance with the following reaction sequence:



In the above formula IIa, the hydroxy protecting group X of formula II is 3,5-di(C_{1-4}alkoxy)-benzoyl as shown. This enables the introduction of both the protecting group and the amide group (which are identical) at step (c). It will however be appreciated that the above scheme may be adapted to permit introduction of any other hydroxy protecting group at step (c).

Step (c) as represented above involves reaction of (III) with a compound of formula V



(V)

wherein R_3 and R_4 have the meanings given for formula I and Z is a leaving group to effect concomitant esterification and amidation.

Suitable compounds of formula V include both halides (Z = halogen, for example chlorine) and anhydrides (Z = 3-(R_3)-5-(R_4)-benzoyloxy). Reaction is appropriately performed at a temperature of from -20° to 50°C, in an inert solvent or diluent such as dichloromethane, and in the presence of a base, for example a dialkylaminopyridine.

Process step (d) comprises dehydrative cyclisation of IV. This may also be achieved by methods known in the art, for example, by reaction of IV with a phosphoroxy trihalide in the presence of an inert solvent or diluent such as acetonitrile at temperatures of from e.g. 50°C to reflux.

By application of the above procedures starting with the racemic compound III, formula I compounds, esters and salts in racemic form may be obtained. Alternatively, starting with the pure [S] or [R] enantiomer of III, the pure or substantially pure [3S] or [3R] formula I compounds, esters and salts may be obtained.

The required starting materials of formulae III (both in racemic and individual [S] and [R] enantiomeric form) are known from the art [cf. Schrecker et al., J. Amer. Chem. Soc. 79, 3827-3828 (1957) and Seki et al., Chem. Pharm. Bull. (Tokyo) 15 (12), 1948-1954 (1967)] or may be prepared analogously to the known compounds.

The following examples are illustrative of the procedures of the present invention:

EXAMPLE 1

Preparation of [3S] 3,4-dihydro-6,7-dimethoxy-1-(3,5-dimethoxy phenyl)-3-hydroxymethyl-isoquinoline, [Step (a)].

A suspension of 98.4g of [3S] 3,4-dihydro-6,7-dimethoxy-3-[(3,5-dimethoxybenzoyloxy)methyl]-1-(3,5-dimethoxyphenyl)-isoquinoline [Formula IIa: all of R_1 to R_4 = methoxy], 5l CH_3OH and 207ml aqueous lithium hydroxide, is stirred for 12 hrs. at room temperature. The obtained solution is concentrated under reduced pressure, treated with ethyl acetate and washed with H_2O/Na_2CO_3. The organic phase is dried over K_2CO_3 and the solvent removed under reduced pressure. The residue is then up in ethyl ether, crystallised, filtered and dried to yield the title compound: m.p. = 59-62°C, α_D^{20} = -55.19° (c=0.5 in CH_3OH).

The obtained free base may be salified and the obtained salt re-crystallised in conventional manner. Thus the title compound is also prepared in the following salt forms:

a) Hydrogen maleinate salt: m.p. = 141-142°C, α_D^{20} = + 154° (c = 0.5 in CH_3OH);

b) Hydrochloride salt: m.p. = 202-204°C, α_D^{20} = + 166° (c = 0.5 in CH_3OH);

c) Hydrogensulfate salt: m.p. = 181-184°C, α_D^{20} = + 152° (c = 0.5 in CH_3OH).

The starting material for the above process is prepared as follows:

Step (c)

204g of 3,5-dimethoxybenzoyl chloride in 700ml CH_2Cl_2 are added to 86g [2S] 2-amino-3-(3,4-dimethoxyphenyl)-propanol [formula III : R_1 and R_2 both = methoxy] and 4.9g 4-dimethyl aminopyridine in 159g triethylamine and 2.3 l

CH_2Cl_2 at 3°C. The reaction mixture is raised to room temperature over 12 hrs., washed with 5% aqueous tartaric acid and 10% $H_2O/NaHCO_3$, and the organic phase dried over Na_2SO_4. The solvent is removed under reduced pressure and the residue crystallised from ethyl ether to yield the product, [2S] 2-(3,5-dimethoxybenzoylamino)-3-(3,4-dimethoxy phenyl)-propyl 3,5-dimethoxy-benzoate [Formula IV: all of R_1 to R_4 = methoxy] : m.p. = 171-174°C.

Step (d)

159g of the product of step (c) in 134g phosphoroxy trichloride and 925ml acetonitrile are heated to reflux for 3hrs. The solvent is removed under reduced pressure the residue treated with 10% $NaHCO_3$ and extracted with ethyl acetate. The organic phase is dried over Na_2SO_4 and solvent removed under reduced pressure. The residue is purified chromatographically on silica gel using hexane/ethyl acetate (1:1) as mobile phase to yield the starting material to step (a): m.p. = 101-108°C.

Racemic 3,4-dihydro-6,7-dimethoxy-1-(3,5-dimethoxyphenyl)-3-hydroxmethyl-isoquinoline is prepared analogously to steps (c) to (a) above starting from racemic 2-amino-3-(3,4-dimethoxy-phenyl)-propanol at step (c): m.p. for the hydrochloride = 214-217°C.

EXAMPLE 2

Preparation of [3S] 3,4-dihydro-1-(3,5-diisopropyloxy-phenyl)-3-hydroxymethyl-6-isopropyloxy-7-methoxy-isoquinoline

The title compound is prepared analogously to the procedures described in example 1, but employing 3,5-diisopropyloxybenzoyl chloride and [2S] 2-amino-3-(3-isopropyloxy-4-methoxyphenyl)-propanol as starting materials at Step (c). $[\alpha]^{20}_D$ for the free base = +155° (c= 0.5 in methanol).

Compounds of formula I, their physiologically-hydrolysable and -acceptable esters and the pharmaceutically acceptable acid addition salts of said compounds and esters (referred to below for convenience collectively as "COMPOUNDS I, ESTERS AND/OR P.A. SALTS") exhibit pharmacological activity and are therefore indicated for use as pharmaceutical agents, e.g. for therapy. In particular they exhibit bronchodilator and asthma-prophylactic as well as anti-inflammatory properties. These properties may be demonstrated in standard tests in vivo and in vitro, for example as follows:

EXAMPLE A: BRONCHODILATOR ACTIVITY

1. Bronchospasmolytic activity in vitro

1.a Relaxation of guinea-pig tracheal smooth muscle

Guinea-pigs (Dunkin-Hartley, 350-500gm) are killed with Pentothal (100mg/kg i.p.). The trachea is dissected and a section 2-3cm in length excised. The trachea is transected in the transverse plane at alternate cartilage plates so as to give rings of tissue 3-5mm in depth. The proximal and distal rings are discarded. Individual rings are mounted vertically on stainless steel supports, one of which is fixed at the base of an organ bath, the other being attached to an isometric transducer. The rings are bathed in Krebs solution (compositon mM: $NaHCO_3$ 25, NaCl 113, KCl 4.7, $MgSO4.7H_2O$ 1.2, KH_2PO_4 1.2, $CaCl_2$ 2.5, Glucose 11.7) at 37 °C and gassed with O_2/CO_2 (95:5, v/v). Rings prepared in this manner, preloaded with 1 g, generate spontaneous tone and, after a period of equilibration (45-60 min.), relax consistently on addition of spasmolytic drugs. To ascertain spasmolytic activity, test substances are dissolved in physiological saline and added in increasing quantities to the organ bath at 5 min. intervals to provide a cumulative concentration-effect curve.

In the above test model COMPOUNDS I, ESTERS AND P.A. SALTS produce concentration-related relaxation of guinea-pig tracheal ring preparations at concentrations of from about 0.001 to 1.0μM. No further relaxation is produced by isoprenaline and relaxation is fully reversed by washing.

1.b Relaxation of human bronchus.

The test is performed analogously to 1.a above but employing rings of human bronchus dissected from lung that has been resected for carcinoma. Dissected material is used immediately or first immersed in total calf serum containing DMSO (1.8μ), slowly frozen to -70°C. and stored in liquid N_2 at -190°C. For use, stored rings are thawed for 30 mins. at room temperature and 3 mins. at 37°C.

In the above test model COMPOUNDS I, ESTERS AND P.A. SALTS produce concentration-related relaxation of human bronchus ring preparations at concentrations of from 0.1 to 10.0μM.

2. Bronchodilator activity in vivo

Guinea pigs (Dunkin-Hartley, male, 400-600g) are anaesthetised with phenobarbital (100-mg/kg i.p.) and pentobarbital (30 mg/kg i.p.) and paralysed with gallamine (10 mg/kg i.m.). Animals are ventilated via a tracheal cannula (10 ml/kg, 1Hz) with a mixture of air and oxygen (1:1 v/v). Blood pressure and heart rate are recorded at the carotid artery. Ventilation is monitored by a Fleisch flow transducer in line with the inspiratory circuit. When making measurements of flow, coincident pressure changes in the thorax are monitored directly via an intrathoracic trochar, permitting display of differential pressure relative to the trachea. From this information in relation to flow and differential pressure, resistance [R_1] and compliance [C_{dyn}] are calculated using a digital respiratory analyzer for each respiratory cycle.

Bombesin [300-600mg/kg] is administered as a bolus injection intravenously, thereby causing bronchospasm which is sustained over several minutes. When bronchospasm has achieved a plateau [at 1-2 mins.], test substance is introduced into the jugular vein via an indwelling cannula. The bronchodilator response is taken as the percentage reduction (measured at both 1 and 3 mins.) of the maximal response to bombesin.

In the above test model COMPOUNDS I, ESTERS AND P.A. SALTS cause significant bronchodilator response at dosages of from about 0.01 to about 0.1 mg/kg i.v..

EXAMPLE B: SUPPRESSION OF AIRWAYS HYPERREACTIVITY

PAF-Treated Animals

Guinea-pigs are anaesthetised and prepared for recording of lung function as described under example A.2. above. Intravenous injection of low dose histamine (1.0 - 1.8 µg/kg) establishes airways sensitivity to spasmogens. Following infusion of PAF (platelet activating factor) over 1 hr. (total dose = 600 ng/kg), injection of low dose bombesin 20 mins. after cessation of infusion reveals development of airways hyperreactivity, which is expressed as the paired difference between the maximal response amplitude before and after PAP exposure.

On administration of COMPOUNDS I, ESTERS AND P.A. SALTS by infusion during PAF exposure at dosages of from about 0.01 to about 0.1 mg/kg, suppression of PAF-induced airways hyperreactivity is observed.

EXAMPLE C: INHIBITION OF HUMAN PHOSPHODIESTERASE (PDE) ISOENZYMES

Phosphodiesterase isoenzymes have been classified according to their tissue distribution, substrate specificity and affinity as well as their susceptibility to selective inhibition by known inhibitor compounds. On this basis, five classes of PDE isoenzymes have been defined: PDE isoenzymes types I through V [Beavo et al., TIPS 11, 150-155 (1990) and Nicholson et al., TIPS 12, 19-27 (1990)]. Type III PDE inhibitors are known to be relaxants of human airways smooth muscle. Type IV PDE inhibitors are reported to have potent anti-inflammatory actions [Murray et al. Agents and Actions Supplements 34, 27-46 (1991)]. Moreover, elevation of PDE isoenzymes corresponding to types III and IV has been reported as a characteristic feaure of leucocytes taken from atopic subjects [Hanafin et al., Drug. Develop. Res., 13, 123-126 (1988)]. Compounds having high selectivity for PDE isoenzymes of Types III and IV may be anticipated to exhibit bronchodilator and asthma prophylactic as well as anti-inflammatory properties.

Citrated human blood was collected and neutrophils obtained by dextran sedimentation, density gradient centrifugation on a mixture of Histopaque 1077 and 1119 with a final density of 1.089g/l and hypotonic lysis of erythrocytes. Human platelets from the same source are washed with PBS (NaCl 140 mM, KCl 2.7 mM, KH_2PO_4 1.5 mM, Na_2HHO_4 8.1 mM, pH 7.4). Neutrophils and platelets are suspended in 10ml of buffer (0.24 M sucrose, 1 mM EDTA, 1mM dithiothreitol, 10mM tris HCl, Ph 7.4) containing the following protease inhibitor solutions: 5 µl/ml of phenylmethylsulphonylfluoride (7 mg/ml in 2-propanol), 1 Nl/ml leupeptin and pepstatin A (1 mg/ml each, in ethanol). After sonication (15 sec at 4°C) using a probe sonicator, homogenates are centrifuged (2200g). The pellet is resuspended in 10 ml of buffer and the sonication repeated. Pooled supernatants are stored at -20°C. Phosphodiesterase activity is assayed by the ion-exchange column method [Thompson et al., Nucleotide Research 10, 69-92 (1979)], using 1µM [^{3}H]-cyclic AMP as substrate.

According to the classification of Beavo et al., loc. cit., PDE activity in neutrophils is categorised as type IV (low K_m cyclic AMP PDE), whereas platelets contain predominantly type III PDE (cyclic GMP-sensitive) and enzyme preparations from human lung comprise type V PDE.

In these preparations, COMPOUNDS I, ESTERS AND P.A. SALTS show greater selectivity for type III, type IV and type V PDE isoenzymes as compared, for example, with the known anti-asthma drug aminophylline.

EXAMPLE D: ANTIINFLAMMATORY ACTIONS - INHIBITION OF SECRETION OF H_2O_2 BY ADHERENT HUMAN NEUROPHILS

Leukocyte-enriched blood cell preparations (buffy coat from 400 ml of blood) are obtained from a blood bank. After hypotonic lysis of erythrocytes, leukocytes are suspended in 20 ml phosphate buffered saline (PBS), distributed into four 15ml polypropylene tubes and underlaid with a discontinuous density gradient consisting of 5ml of Histopaque 1089 (from a mixture of 12ml of Histopaque 1119 and 30ml of Histopaque 1077). Centrifugation (10 min. at 2000g, room temperature) yields a band on the interface consisting of mononuclear blood cells and a pellet of >90% neutrophils as verified by differential cell count of May-Grünwald stained smears. Neutrophils are suspended in Krebs-Ringer at 6 x 10^5/ml. 96 well microtitre plates are coated with 50µl/well of a 1µg/ml solution of fibronectin in PBS and incubated for 4h at 37°C.

Before use, wells are rinsed once with 100µl Krebs-Ringer. Each well is loaded with inhibitor in 0.6% dimethylsulfoxide (DMSO) (final concentration of DMSO 0.15%, showing no effect when compared to wells without DMSO), 42 pmol N-formyl-Met-Leu-Phe fMLP, 5µg horseradish peroxidase, 50µg sodium azide, 5µg of scopoletin and 15'000 neutrophils in a final volume of 0.1 ml. Plates are held at 37°C during 2 hours, after which fluorescence (excitation 365 nm, emission 460 nm) is read.

To calculate the effect of inhibitors, DMSO-treated controls are used to represent 0% inhibition, and wells without cells are used to represent 100% inhibition (i.e. no fluorescence loss).

The chemotactic peptide fMLP induces secretion of large amounts of hydrogen peroxidase from adherent human neutrophils, or reaction that can be detected by scopoletin oxidation indicating cell activation.

In this test method, COMPOUNDS I, ESTERS AND P.A. SALTS strongly inhibit H_2O_2 secretion at concentrations of the order of 1.0 to 10.0 µM.

In addition to the foregoing, general pharmacological testing indicates that COMPOUNDS I, ESTERS AND P.A. SALTS exhibit a marked and surprisingly improved profile in relation to intended therapeutic uses compared with other known compounds, e.g. of related structure, for example, reduced influence on behavioural response, e.g. in male OFA mice and/or reduced cardiovascular side effect, for example in relation to hemodynamic parameters. COMPOUNDS I, ESTERS AND P.A. SALTS also show advantage as exhibited, e.g. in toxicity acute tolerability studies in the dog and in primates.

Having regard to their bronchodilator activity as well as their profile in relation to PDE isoenzyme inhibition, COMPOUNDS I, ESTERS AND P.A. SALTS are indicated for use as bronchodilators, e.g. for the treatment of broncho-constriction (chronic or acute). As bronchodilators they are, in particular, indicated for use for the symptomatic treatment, of obstructive or inflammatory airways disease.

Having regard to their activity in inhibiting airways hyperreactivity or in diminishing basal or on-going airways hyperreactivity, their anti-inflammatory properties and their profile in relation to PDE isoenzyme inhibition, COMPOUNDS I, ESTERS AND P.A. SALTS are are indicated for use in the prophylactic treatment of obstructive or inflammatory airways disease. Thus COMPOUNDS I, ESTERS AND P.A. SALTS are indicated for use prophylactically, suitably by continued and regular administration over longer periods of time, to provide advance protection against recurrence of bronchoconstrictor attack consequential to obstructive or inflammatory airways disease including specific such diseases as hereinafter specified or for the control, restriction or reversal of basal status of such disease.

The words "treatment" and "treating" as used throughout the present specification and claims in relation to obstructive or inflammatory airways disease are to be understood accordingly as including both symptomatic and prophylactic modes of treatment or therapy as discussed above.

In accordance with the foregoing the present invention also provides:

IA. A method of effecting bronchodilatation in a subject in need thereof which method comprises administering to said subject an effective amount of a COMPOUND I, ESTER OR P.A. SALT; as well as

IB. A method of treating, e.g. inhibiting or ameliorating, airways hyperreactivity in a subject in need thereof, which method comprises administering to said subject effective amount of a COMPOUND I, ESTER OR P.A. SALT.

In the alternative the present provides:

II. A COMPOUND I, ESTER OR P.A. SALT for use as a pharmaceutical, for example for use as a bronchodilator or for use in treating, e.g. inhibiting or ameliorating airways hyperreactivity.

The present invention in particular provides a method, e.g. as defined under IA and/or IB above, for the treatment of obstructive or inflammatory airways disease including, asthma, pneumoconiosis and chronic obstructive airways disease (COAD) as well as exacerbation of airways hyperreactivity consequent to other drug therapy.

The present invention especially provides a method for the treament of asthma of whatever type or genesis. It is applicable to both intrinsic and, especially, extrinsic asthma. It is especially applicable to the treatment of allergic (atopic, i.e. IgE-mediated), asthma. It is also applicable to the treatment of non-atopic, as well as bronchitic asthma, excercise induced asthma, occupational asthma, asthma induced following bacterial infection and other non-allergic asthmas. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g. of less than 4 or 5 years of age, exhibiting wheezing symptoms, in particular at night, and diagnosed or diagnosable as "wheezy infants", an established patient category of major medical concern and now more correctly identified as incipient or early-phase asthmatics. (For convenience this particular asthmatic condition is referred to as "wheezy-infant syndrome").

The present invention also provides a method for the treatment of pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and, in particular, byssinosis.

The present invention further provides a method for the treatment of COAD or exacerbation of airways hyperreactivity consequent to other drug therapy, in particular other inhaled drug therapy, for example, β-agonist bronchodilator drug therapy.

The present invention also provides a method, e.g. as defined under IA above for the tratment of chronic or acute bronchoconstriction or airways obstruction, as well as of diseases or conditions characterised by such bronchoconstriction, for example chronic obstructive pulmonary disease (COPD) including chronic bronchitis and pulmonary emphysema or dyspnea associated therewith. The present invention is also applicable to the treatment of bronchitis of whatever type or genesis, including, for example, acute bronchitis, arachidic bronchitis, catarrhal bronchitis, chronic bronchitis, croupous bronchitis, phthinoid bronchitis and so forth.

The present invention thus further provides:

II A method for the treatment (including symptomatic and/or prophylactic treatment as the case may be) of any disease or condition as hereinbefore set forth, which method comprises administering to a subject in need thereof an effective amount of a COMPOUND I, ESTER OR P.A. SALT; as well as

III A COMPOUND I, ESTER OR P.A. SALT for use in any disease or condition as hereinbefore set forth.

Having regard to their profile in relation to inhibition of PDE isoenzymes, in particular their profile as type IV PDE inhibitors, COMPOUNDS I, ESTERS AND P.A. SALTS are also indicated for use as type IV PDE inhbitors, for example: for the treatment of inflammatory and allergic diseases such as rhinitis, conjunctivitis, atopic dermatitis, urticaria and gatro-intestinal allergies; as vasodilators, e.g. for the treatment of angina, hypertension, congestive heart failure and multi-infarct dementia; and for the treatment of other conditions where PDE IV inhibition is indicated, for example, depression, conditions and diseases characterised by impaired cognitive function including Alzheimer's disease, Parkinson's disease, rheumatic and other inflammatory disease, stroke, heterograft rejection and other immune related diseases, in particular autoimmune diseases such as autoimmune haematological disorders (including e.g. haemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), systemic lupus erythematosus, polychondritis, sclerodoma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (including e.g. ulcerative colitis and Crohn's disease) endocrine ophthalmopathy, Graves disease, sarcoidosis, multiple sclerosis, primary billiary cirrhosis, juvenile diabetes (diabetes mellitus type I), uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis and glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy). COMPOUNDS I, ESTERS AND P.A. SALTS are further indicated for use in the treatment or therapy of adult respiratory distress syndrome (ARDS) and bronchiolitis.

COMPOUNDS I, ESTERS AND P.A. SALTS are also indicated for use as anti-tumor agents as may, for example, be indicated by their activity in human cell line cytotoxicity tests against human tumor cell lines as well as clonogenic assay.

Dosages employed in practicing the various methods of the present invention will of course vary depending, e.g., on the particular condition to be treated, the particular COMPOUND I, ESTER AND P.A. SALT employed, the mode of administration and the therapy desired. In general however an indicated daily dosage for oral administration, in particular as bronchodilator agents or as agents for the inhibition or amelioration of airways hyperreactivity, e.g. for such use in diseases or conditions are hereinbefore described, in particular for use in obstructive or inflammatory airways disease, especially asthma, will be in the range of from about 10 to about 200mg, in particular from about 50 to 100mg conveniently administered once or in divided doses 2 to 4x/day or in sustained release form. Unit dosage forms for oral administration thus suitably comprise from about 2.5 to about 200, in particular from about 12.5 to about 50 or 100mg of COMPOUND I, ESTER OR P.A. SALT, together with a pharmaceutically acceptable diluent or carrier therefor.

COMPOUNDS I and ESTERS may be administered in free base form or in pharmaceutically acceptable acid addition salt form. Such salts (i.e. P.A. SALTS) exhibit the same order of activity as the free bases.

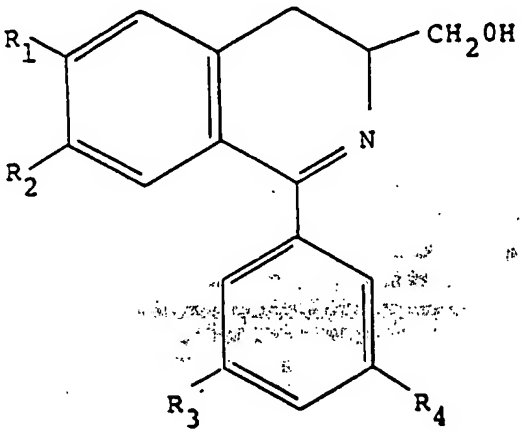
COMPOUNDS I, ESTERS OR P.A. SALTS may be administered by any conventional route, suitable or appropriate to the condition or disease to be treated, e.g. nasally, enterally, topically, orally, e.g. in the form of tablets or capsules, or parenterally, e.g. in the form of injectable solutions or suspensions. They may also, in particular, be administered by the pulmonary route, especially where diseases or conditions of the airways are to be treated, for example for bronchodilator effect or for the inhibition or amelioration of airways hyperreactivity.

In accordance with the foregoing the present invention also provides: a pharmaceutical composition comprising a COMPOUND I, ESTER OR P.A. SALT together with a pharmaceutically acceptable diluent carrier therefor, e.g. for use in any method as defined above. Such compositions may be manufactured in conventional manner.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. A compound of formula I



(I)

wherein

R_1 to R_4 are each independently C_{1-4}alkoxy,

or physiologically-hydrolysable and -acceptable ester thereof,
or acid addition salt of such a compound or ester.

2. A compound of formula I as illustrated in claim 1 wherein R_1 to R_4 are each methoxy, or physiologically-hydrolysable and -acceptable ester thereof or acid addition salt of such a compound or ester.

3. A compound as claimed in claim 1 or 2 in [3S] enantiomeric form, or physiologically-hydrolysable and -acceptable ester thereof or acid addition salt of such a compound or ester.

4. [3S] 3,4-dihydro-6,7-dimethoxy-1-(3,5-dimethoxy-phenyl)-3-hydroxymethyl-isoquinoline or an acid addition salt thereof.

5. [3S] 3,4-dihydro-1-(3,5-diisopropyloxy-phenyl)-3-hydroxymethyl-6-isopropyloxy-7-methoxy-isoquinoline or an acid addition salt thereof.

6. A pharmaceutical composition comprising a compound or ester as claimed in any one of claims 1 to 5, or a pharmaceutically acceptable acid addition salt of such a compound or ester, together with a pharmaceutically acceptable diluent or carrier therefor.

7. A compound or ester as claimed in any one of claims 1 to 5, or a pharmaceutically acceptable acid addition salt of such a compound or ester for use as a phamaceutical.

8. A compound, ester or salt as claimed in claim 1 for use as a bronchodilating agent or for the inhibition or amelioration of airways hyperreactivity.

9. A compound, ester or salt as claimed in claim 1 for use in the treatment of obstructive or inflammatory airways disease.

10. A process for the production of a compound of formula I as defined in claim 1 or a physiologically-hydrolysable and -acceptable ester thereof or an acid addition salt of such a compound or ester which process comprises.

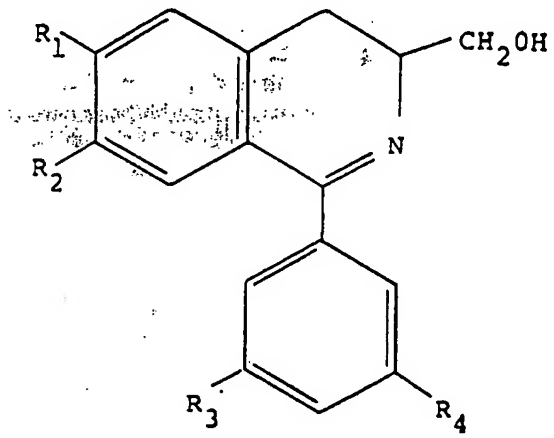
a) for the production of a compound of formula I as defined in claim 1, removing the protecting group from a compound of formula I as defined in claim 1 in 3-hydroxy protected form; or

b) for the production of a physiologically-hydrolysable and -acceptable ester of a compound of formula I as defined in claim 1, esterifying a compound of formula I as defined in claim 1; and

recovering the obtained compound of formula I or ester in free or acid addition salt form.

Claims for the following Contracting States : ES, GR

1. Process for the production of a compound of formula I



(I)

wherein

R_1 to R_4 are each independently C_{1-4}alkoxy,

or physiologically-hydrolysable and -acceptable ester thereof,
or acid addition salt of such a compound or ester which process comprises.

a) for the production of a compound of formula I as defined above, removing the protecting group from a compound of formula I as defined which is in 3-hydroxy protected form; or

b) for the production of a physiologically-hydrolysable and -acceptable ester of a compound of formula I as defined above, esterifying a compound of formula I as defined in claim 1; and

recovering the obtained compound of formula I or ester in free or acid addition salt form.

2. Process according to claim 1 wherein the compound of formula I is in [3S] enantiomeric form.

3. Process according to claim 1 or 2 wherein in formula I R_1 to R_4 are each methoxy.

4. Process according to claim 1 or 2 wherein in formual I, R_1, R_3 and R_4 are each isopropyloxy and R_2 is methoxy.

5. A compound of formula I, ester or salt as defined in claim 1 whenever prepared by a process as claimed in claim 1.

6. A compound of formula I, ester or salt as defined in claim 1 in [3S] enantiomeric form whenever prepared by a process as claimed in claim 2.

7. [3S] 3,4-dihydro-6,7-dimethoxyl-1-(3,5-dimethoxy-phenyl)-3-hydroxymethyl-isoquinoline or an acid addition salt thereof, whenever prepared by a process as claimed in claim 4.

8. [3S] 3,4-dihydro-1-(3,5-diisopropyloxy-phenyl)-3-hydroxymethyl-6-isopropyloxy-7-methoxy-isoquinoline or an acid addition salt thereof whenever prepared by a process as claimed in claim 5.

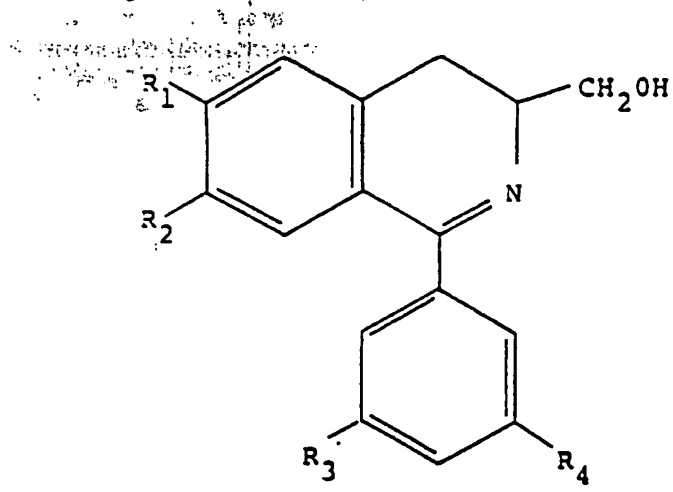
9. A pharmaceutical composition comprising a compound or ester as defined in any one of claims 5 to 8 or a pharmaceutically acceptable acid addition salt of such a compound or ester, together with a pharmaceutically acceptable diluent or carrier therefor.

10. A compound or ester as claimed in any one of claims 5 to 8, or a pharmaceutically acceptable acid addition salt thereof for use as a pharmaceutical.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Verbindung der Formel I



(I)

worin

R_1 bis R_4 jeweils unabhängig für C_{1-4} Alkoxy stehen,

oder ein physiologisch-hydrolysierbarer und -annehmbarer Ester hiervon,
oder ein Säureadditionssalz einer solchen Verbindung oder eines solchenEsters.

2. Verbindung der Formel I nach Anspruch 1, worin R_1 bis R_4 jeweils für Methoxy stehen, oder ein physiologisch - hydrolysierbarer und -annehmbarer Ester hiervon oder ein Säureadditionssalz einer solchen Verbindung oder eines solchen Esters.

3. Verbindung nach Anspruch 1 oder 2 in Form des [3S]-Enantiomers, oder ein physiologisch - hydrolysierbarer und -annehmbarer Ester hiervon oder ein Säureadditionssalz einer solchen Verbindung oder eines solchen Esters.

4. [3S]-3,4-Dihydro-6,7-dimethoxy-1-(3,5-dimethoxyphenyl)-3-hydroxymethylisochinolin oder ein Säureadditionssalz hiervon.

5. [3S]-3,4-Dihydro-1-(3,5-diisopropyloxyphenyl)-3-hydroxymethyl-6-isopropyloxy-7-methoxy-isochinolin oder ein Säureadditionssalz hiervon.

6. Pharmazeutische Zusammensetzung, die eine Verbindung oder einen Ester nach einem der Ansprüche 1 bis 5 enthält, oder ein pharmazeutisch annehmbares Säureadditionssalz einer solchen Verbindung oder eines solchen Esters, zusammen mit einem pharmazeutisch annehmbaren Verdünnungsmittel oder Träger hierfür.

7. Verbindung oder Ester nach einem der Ansprüche 1 bis 5, oder ein pharmazeutisch annehmbares Säureadditionssalz einer solchen Verbindung oder eines solchen Esters zur Verwendung als Pharmazeutikum.

8. Verbindung, Ester oder Salz nach Anspruch 1 zur Verwendung als bronchodilatatorisches Mittel oder zur Hemmung oder Verbesserung der Atemwegshyperreaktivität.

9. Verbindung, Ester oder Salz nach Anspruch 1 zur Verwendung bei der Behandlung einer obstruktiven oder entzündlichen Atemwegserkrankung.

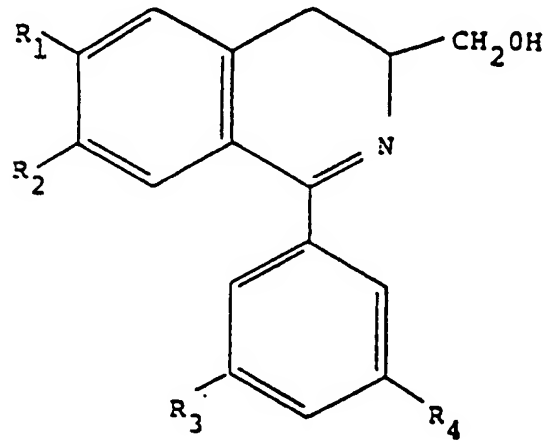
10. Verfahren zur Herstellung einer Verbindung der Formel I nach Anspruch 1 oder eines physiologisch - hydrolysierbaren und -annehmbaren Esters hiervon oder eines Säureadditionssalzes einer solchen Verbindung oder eines solchen Esters, wobei das Verfahren gekennzeichnet ist durch

    a) zur Herstellung einer Verbindung der Formel I nach Anspruch 1, Entfernung der Schutzgruppe von einer Verbindung der Formel I nach Anspruch 1 in 3-Hydroxy- geschützter Form, oder
    b) zur Herstellung eines physiologisch - hydrolysierbaren und -annehmbaren Esters einer Verbindung der Formel I nach Anspruch 1, Veresterung einer Verbindung der Formel I nach Anspruch 1, und

Gewinnung der erhaltenen Verbindung der Formel I oder des Esters in freier Form oder in Form des Säureadditionssalzes.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung einer Verbindung der Formel I



(I)

worin

R_1 bis R_4 jeweils unabhängig für C_{1-4} Alkoxy stehen,

oder eines physiologisch - hydrolysierbaren und -annehmbaren Esters hiervon,
oder eines Säureadditionssalzes einer solchen Verbindung oder eines solchen Esters, wobei das Verfahren gekennzeichnet ist durch

a) zur Herstellung einer Verbindung der Formel I wie oben definiert, Entfernung der Schutzgruppe von einer Verbindung der Formel I, wie oben definiert, welche in 3-Hydroxy geschützter Form vorliegt, oder
b) zur Herstellung eines physiologisch - hydrolysierbaren und -annehmbaren Esters einer Verbindung der Formel I wie oben definiert, Veresterung einer Verbindung der Formel I, nach Anspruch 1, und Gewinnung der erhaltenen Verbindung der Formel I oder des Esters in freier Form oder in Form des Säureadditionssalzes.

2. Verfahren nach Anspruch 1, worin die Verbindung der Formel I in Form des [3S]-Enantiomers vorliegt.

3. Verfahren nach Anspruch 1 oder 2, worin in Formel I R_1-R_4 jeweils für Methoxy stehen.

4. Verfahren nach Anspruch 1 oder 2, worin in Formel I, R_1, R_3 und R_4 jeweils für Isopropyloxy stehen und R_2 für Methoxy steht.

5. Verbindung der Formel I, eines Esters oder Salzes nach Anspruch 1, falls durch ein Verfahren nach Anspruch 1 hergestellt.

6. Verbindung der Formel I, eines Esters oder Salzes nach Anspruch 1 in Form des [3S]-Enantiomers, falls durch ein Verfahren nach Anspruch 2 hergestellt.

7. [3S]-3,4-Dihydro-6,7-dimethoxy-1-(3,5-dimethoxyphenyl)-3-hydroxymethylisochinolin oder ein Säureadditionssalz hiervon, falls durch ein Verfahren nach Anspruch 4 hergestellt.

8. [3S]-3,4-Dihydro-1-(3,5-diisopropyloxyphenyl)-3-hydroxymethyl-6-isopropyloxy-7-methoxy-isochinolin oder ein Säureadditionssalz hiervon, falls durch ein Verfahren nach Anspruch 5 hergestellt.

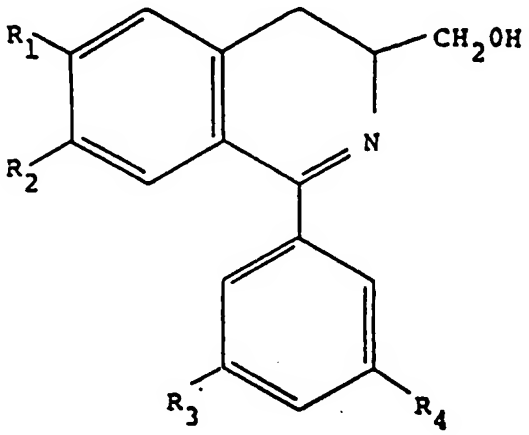
9. Pharmazeutische Zusammensetzung, die enthält eine Verbindung oder einen Ester nach einem der Ansprüche 5 bis 8, oder ein pharmazeutisch annehmbares Säureadditionssalz einer solchen Verbindung oder eines solchen Esters, zusammen mit einem pharmazeutisch annehmbaren Verdünnungsmittel oder Träger hierfür.

10. Verbindung oder Ester nach einem der Ansprüche 5 bis 8, oder ein pharmazeutisch annehmbares Säureadditionssalz hiervon, zur Verwendung als Pharmazeutikum.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Un composé de formule I



(I)

dans laquelle les symboles R_1 à R_4 signifient chacun indépendamment un groupe alcoxy en C_1-C_4,
ou un ester physiologiquement hydrolysable et acceptable de ce composé,
ou un sel d'addition d'acide d'un tel composé ou ester.

2. Un composé de formule I tel qu'illustré à la revendication 1, où les symboles R_1 à R_4 signifient chacun un groupe méthoxy, ou un ester physiologiquement hydrolysable et acceptable de ce composé, ou un sel d'addition d'acide d'un tel composé ou ester.

3. Un composé selon la revendication 1 ou 2 sous forme énantiomère [3S], ou un ester physiologiquement hydrolysable et acceptable de ce composé, ou un sel d'addition d'acide d'un tel composé ou ester.

4. La [3S] 3,4-dihydro-6,7-diméthoxy-1-(3,5-diméthoxyphényl)-3-hydroxyméthyl-isoquinoléine ou un sel d'addition d'acide de ce composé.

5. La [3S] 3,4-dihydro-1-(3,5-diisopropyloxy-phényl)-3-hydroxyméthyl-6-isopropyloxy-7-méthoxy-isoquinoléine ou un sel d'addition d'acide de ce composé.

6. Une composition pharmaceutique comprenant un composé ou un ester tels que spécifiés à l'une quelconque des revendications 1 à 5, ou un sel d'addition d'acide pharmaceutiquement acceptable d'un tel composé ou ester, en association avec un diluant ou véhicule pharmaceutiquement acceptable.

7. Un composé ou un ester tels que spécifiés à l'une quelconque des revendications 1 à 5, ou un sel d'addition d'acide pharmaceutiquement acceptable d'un tel composé ou ester, pour une utilisation comme médicament.

8. Un composé, un ester ou un sel tels que spécifiés à la revendication 1 pour une utilisation comme agent bronchodilatateur ou pour l'inhibition ou l'amélioration de l'hyperréactivité des voies respiratoires.

9. Un composé, un ester ou un sel tels que spécifiés à la revendication 1 pour une utilisation dans le traitement d'une maladie obstructive ou inflammatoire des voies respiratoires.

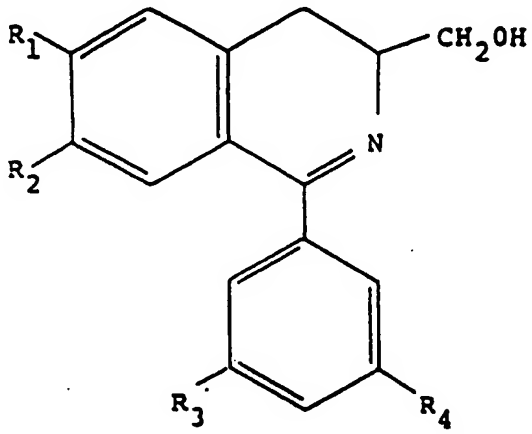
10. Un procédé de préparation d'un composé de formule I tel que défini à la revendication 1 ou d'un ester physiologiquement hydrolysable et acceptable de ce composé ou d'un sel d'addition d' acide d'un tel composé ou ester, procédé caractérisé en ce que

a) pour la préparation d'un composé de formule I tel que défini à la revendication 1, on élimine le groupe protecteur d'un composé de formule I tel que défini à la revendication 1 dont le groupe 3-hydroxy est sous forme protégée ou bien
b) pour la préparation d'un ester physiologiquement hydrolysable et acceptable d'un composé de formule I tel que défini à la revendication 1, on estérifie un composé de formule I tel que défini à la revendication 1, et

on récupère le composé obtenu de formule I ou l'ester sous forme libre ou sous forme d'un sel d'addition d'acide.

Revendications pour les Etats contractants suivants : ES, GR

1. Un procédé de préparation d'un composé de formule I



(I)

dans laquelle les symboles R_1 à R_4 signifient chacun indépendamment un groupe alcoxy en C_1-C_4,
ou d'un ester physiologiquement hydrolysable et acceptable de ce composé,
ou d'un sel d'addition d'acide d'un tel composé ou ester, caractérisé en ce que

a) pour la préparation d'un composé de formule I tel que défini ci-dessus, on élimine le groupe protecteur d'un composé de formule I tel que défini ci-dessus dont le groupe 3-hydroxy est sous forme protégée ou bien
b) pour la préparation d'un ester physiologiquement hydrolysable et acceptable d'un composé de formule I tel que défini ci-dessus, on estérifie un composé de formule I tel que défini ci-dessus, et

on récupère le composé obtenu de formule I ou l'ester sous forme libre ou sous forme d'un sel d'addition d'acide.

2. Un procédé selon la revendication 1 où le composé de formule I est sous forme énantiomère [3S].

3. Un procédé selon la revendication 1 ou 2 où, dans la formule I, les symboles R_1 à R_4 signifient chacun un groupe méthoxy.

4. Un procédé selon la revendication 1 ou 2 où, dans la formule I, les symboles R_1, R_3 et R_4 signifient chacun un groupe isopropyloxy et R_2 signifie un groupe méthoxy.

5. Un composé de formule I, un ester ou un sel tels que définis à la revendication 1 et préparés selon un procédé tel que défini à la revendication 1.

6. Un composé de formule I, un ester ou un sel tels que définis à la revendication 1, sous forme énantiomère [3S] et préparés selon un procédé tel que défini à la revendication 2.

7. La [3S] 3,4-dihydro-6,7-diméthoxy-1-(3,5-diméthoxyphényl)-3-hydroxyméthyl-isoquinoléine ou un sel d'addition d'acide de ce composé préparés selon un procédé tel que défini à la revendication 4.

8. La [3S] 3,4-dihydro-1-(3,5-diisopropyloxy-phényl)-3-hydroxyméthyl-6-isopropyloxy-7-méthoxy-isoquinoléine ou un sel d'addition d'acide de ce composé préparés selon un procédé tel que défini à la revendication 5.

9. Une composition pharmaceutique comprenant un composé ou un ester tels que spécifiés à l'une quelconque des revendications 5 à 8, ou un sel d'addition d'acide pharmaceutiquement acceptable d'un tel composé ou ester, en association avec un diluant ou véhicule pharmaceutiquement acceptable.

10. Un composé ou un ester tels que spécifiés à l'une quelconque des revendications 5 à 8, ou un sel d'addition d'acide pharmaceutiquement acceptable d'un tel composé ou ester, pour une utilisation comme médicament.